JOURNAL OF THE
American Geriatrics Society
Official Journal of the
American Geriatrics Society · American Therapeutic Society · Texas Geriatrics Society

VOLUME VI | *May, 1958* | NUMBER 5

PANEL DISCUSSION ON TRANQUILIZING DRUGS IN THE CLINICAL MANAGEMENT OF MENTAL DISEASE IN GERIATRIC PATIENTS*

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MODERATOR FRANK J. AYD, JR.: This discussion will be devoted to the use of tranquilizing drugs in the management of mental disease in geriatric patients.

An avalanche of reports devoted to the use of tranquilizing drugs has appeared in this country and abroad since 1952. The panel comprises physicians who have had considerable clinical experience with many of these compounds, and thus are entitled to speak with authority.

We encourage you to ask questions. We may not answer all of them, but perhaps, by combining resources, we shall be able to give a satisfactory response.

We shall ask Dr. Schiele to make a few remarks as a basis for our discussion. Dr. Schiele.

DR. BURTRUM C. SCHIELE: As background, I shall present a brief review of present concepts of the nature of personality disorders in later life. First, may I quote a few sentences from a 1947 textbook of psychiatry which gives the traditional definition and description of senile psychosis. "Senile psychoses are progressive mental disorders due to pathological age, marked by defective mental functioning, and notably by impairment of recent memory." The section on Etiology lists: "Brain destruction conditioned by cerebral arterial sclerosis, and other factors including old age, and possibly by toxic and hereditary influ-

* Conducted at the Graduate Symposium on Geriatric Medicine of The American Geriatrics Society and The American Academy of General Practice, Rhode Island and New York Chapters, New York City, November 19 and 20, 1956.

ences." This book furnishes case examples and ends with a short paragraph on treatment which concludes with the statement that institutionalization may be the kindest thing for all concerned.

This is the traditional view of senile psychoses. Often, unwittingly, many of us tend to think of all mental disorders of aging in this sense. I should like to mention a few other things in our current thinking.

Until recent years, it was customary to ascribe all behavior disturbances to senile decay. It was taken for granted, for example, that reminiscences were due to failure of recent memory, that loss of interest in dress was due to cerebral deterioration, and that tearfulness was due to damage in the cortex and diencephalon. This attitude was in part based upon fact. Anatomic degeneration does play a highly significant role by directly producing certain symptoms, particularly the progressive loss of memory and other signs of intellectual decline characteristic of an aging person.

In the past, physicians avidly sought anatomic explanations for all mental illness. In senile patients, definite positive findings were evident. Errors were made, however, in assuming that organic changes directly caused all of the mental symptoms exhibited by the nervous or disturbed older person. Except in extreme cases, there is poor correlation between changes found in the brain at necropsy and the behavior of the patient. One cannot reliably infer the degree of brain deterioration from senile behavior nor estimate the level of behavior from a study of the brain after death. In other words, although marked pathologic changes occur in the brain, they are not limited to patients with abnormal behavior. They also occur in older people whose behavior is normal and in those whose behavior deviations are slight.

Clinical findings show a similar lack of correlation. Patients with severe progressive memory disturbances and other intellectual losses do not necessarily show the most severe disturbances of behavior. The person's ability to accept and adjust to the decline of memory and other changes is also important in determining his clinical response. A calm, confident person may anticipate the effects of age and adjust to them much better than one who has always been tense, insecure and dissatisfied.

Still other evidence exists that psychogenic and personal factors are important. The histories of disturbed old people show a much higher incidence of poor adjustment earlier in life than do the histories of more normal oldsters. For example, they may have had poor relations with their children, narrow interests, and few hobbies.

The clinical course reveals a more hopeful situation than was formerly recognized. Senile persons often recover from psychotic episodes. In Minnesota, we recently had occasion to follow 36 patients for six years after discharge from our hospital. Though many of them died in the meantime, 26 per cent had no recurrence of personality disturbance during the six-year period or until the time of death.

When disorders of behavior develop in the aged, they may differ little from those found at other years in life, except for differences resulting from waning

physiologic competence. The same kind of functional mental illnesses may develop in old people as in middle-aged and younger persons. It needs to be emphasized that we must be aware of other types of organic disturbances in addition to the senile and arteriosclerotic conditions of later life. It is not uncommon for a physician to assume that an elderly patient's personality changes and difficulties are due to senility, whereas the patient may be suffering from a brain tumor, subdural hematoma, or some kind of toxic delirium. We must keep in mind that old people are fragile and that it sometimes takes little to upset their equilibrium. Dehydration, poor nutrition, and other things of this sort may tip the balance just enough that the old person may decompensate as far as his personality is concerned and require care and treatment. Moreover, any of the various functional illnesses may persist, recur, or flower at a late stage in life.

I should like to stress that brain damage is reflected in memory disturbance, disorientation and intellectual loss, but that depression, paranoid ideas, anxiety states, hypochondriasis and the like are not the direct result of brain damage.

Let us look at the psychogenic factors. Old people are subject to the same psychologic stresses and anxieties as when they were younger. The infirmities of age, and the social and economic limitations that these impose, constitute an additional and progressive stress. Take, for example, the decline in strength and endurance, or the loss of physical attractiveness. The latter occurs just when a person needs it most. Think how devastating this may be to a man or woman who has relied on good looks or physical prowess as the chief source of acceptance and self-esteem. Add to this, reduced visceral function, diminution in the various senses (particularly of sight and hearing), reduced sexual function, failing memory and increased lability of emotions, and one can see why an old person may feel restless, unhappy, unwanted and in the way.

The problems that an old person must face may have a pronounced emotional impact unless he has prepared for these inevitable changes. Thus, an old person is vulnerable to psychologic stress, just as he is to physical stress, because of his low reserves and his loss of flexibility. Little things may tip the balance—things that he would have taken in his stride in younger years. If, for example, a new highway project comes through your neighborhood and your house must be torn down, you have to move. A young person can adjust to this easily, whereas an older person may have great difficulty in reassociating in a new neighborhood.

As he cannot deal so effectively with the future nor the present, he tends to overvalue the past. Under such stresses, previously existing neurotic patterns tend to reassert themselves. This may be one of the reasons why neurotic complaints among the aged are so common. The kind of disorder that occurs will likely be determined by the personality organization. Even in clearly organic cases, the clinical picture is partly determined by the previous personality makeup. For example, in delirium, the fact that delirium exists is determined by the toxic agent, whatever that may be, but the mental content of the delirium is largely determined by the patient's past experiences. As a gross example, let us take the case of delirium developing in a Chinaman during his first visit to

New York. You would not expect him to voice his hallucinations in English. His hallucinations would be in Chinese and would largely concern Chinese phenomena.

To summarize this point, I should like to read a quotation from a recent article by Dr. Bart entitled, "Age Introduces Stress Into the Family." He says "Man becomes, in a sense, what he has been. His old age adjustments are very much those of his childhood and youth, and his old age fears and anxieties are likely to be reactivations from childhood." Cicero said the same thing in another way centuries ago: "Those with simple desires and good dispositions find old age easy to take." "Those who do not show wisdom and virtue in their youth are prone to attribute to old age those infirmities which are actually produced by former irregularities."

MODERATOR AYD: Thank you, Dr. Schiele. With that foundation as to why we are called upon to treat certain symptomatic conditions, we are in a position to approach the most important aspect of the discussion, namely, how to treat and manage the various symptomatic conditions with drugs.

Dr. Ernest Parsons of St. Louis will tell us something about the drugs, how they act, how he has used them in private practice, and what he has encountered.

DR. ERNEST H. PARSONS: Thank you, Dr. Ayd.

Dr. Schiele has sketched the standard concept of the clinical syndrome present in the so-called senile patient. Our application of tranquilizing drugs in the geriatric patient has been based upon our concept of the basis for the syndrome. If the mental illnesses, or aberrations, seen in psychiatric patients were due wholly to the destruction of brain tissue, the value of tranquilizing agents would be limited in most cases and futile in others. We know, however, as Dr. Schiele has indicated, that many of the psychiatric aspects of the geriatric syndrome arise, not from tissue destruction but from psychologic causes. My own concept of the syndrome (and I am sure yours also) is somewhat personally oriented. It seems to me that, when we reach the stage in life of decreasing effectiveness, we first find that we are not needed and then begin to develop protective mechanisms. Observing this in patients, I have at times been amused at the extent to which these defense mechanisms are elevated and the strength with which they are clasped by the patient. I think of a business man who had been quite effective throughout his life. When retired at a specific, rigid age, his previous effectiveness and usefulness seemed almost to dissolve in a syndrome of sputtering defense of "the good old days."

In working with older patients—whom I prefer to refer to as more mature patients (this being part of my personal defense mechanism)—we are dealing with more complex clinical problems than is the case of younger persons. In simple terms, more has happened to these people than has happened to younger persons, and more has happened to their physiologic and integrating mechanisms. The assets of a previous pattern of behavior are of distinct value therapeutically. Because of these, we believe that the use of tranquilizing agents has a valuable place in the management of older people.

The use of drugs to suppress mental activity in these patients who have the

asset of an established personality and who have the additional asset of a pattern of behavior with many years of experience substantiating the personality structure would, in our opinion, be most unwise. In the young person it may indeed at times be imperative that complete suppression be obtained, but in the older person the problem is that of reorganization rather than suppression. This is a distinction that must be made in considering the psychiatric management of the geriatric patient.

In using tranquilizing agents, regardless of chemical composition, it is important to recall that they function primarily as blocking agents. All of these drugs inhibit or block certain parts of the reflex arcs, primarily in the midbrain, but to some extent peripherally. Meprobamate and drugs in this series of chemicals exert their blocking action peripherally, with central effects only as the concentration of the drug rises. On the other hand, chlorpromazine and reserpine are primarily effective in the midbrain, and the peripheral side-effects are only secondary. The interesting point neurophysiologically is that the integrating system functions more effectively when the disadvantageous midbrain reflex arcs are inhibited.

I find it easiest to think of these inhibited reflexes as those which permit the patient to interpret disturbing stimuli in a disadvantageous manner. I recognize that this is too simple a statement, but it is a convenient way to think of the phenomenon observed when we utilize tranquilizing agents in geriatric patients. The inhibition of disadvantageous reflexes is of clinical value. Unfortunately, as side-effects, other disadvantageous reflex changes may occur simultaneously. Thus, interruption of the righting reflex may produce considerable instability in these patients. If the righting reflexes are interrupted in a patient with marked hypotension, an orthopedic complication may occur as a result of the combination of the two, for the patient may fall and incur a fracture. A side-effect on the gastro-intestinal tract must also be borne in mind, particularly with the reserpine series of drugs which produce a secondary increase in secretory function. In contrast, there is a decrease in gastro-intestinal motility with chlorpromazine, so that constipation may be a complication. The end-result of therapy with the blocking or tranquilizing agents is to permit more effective use of the so-called reticular activating system—a neurophysiologic pathway characterized by a flow of impulses from the body to the upper centers in the brain, thus controlling awareness. Tranquilizing drugs act by this pathway to improve the patient's power of concentration and ability to maintain attention, that is, to be more effective. As this occurs, the patient usually becomes more comfortable.

Blocking of disquieting stimuli (disadvantageous reflex arcs in the midbrain) is not the same as suppressing mental activity. In other words, the tranquilizing agents are not sedatives. They increase the effectiveness of the mature patient by blocking adverse stimuli, but at the same time they enhance the capacity for attention, concentration, and effective responses to appropriate stimuli. Upon this chemically induced neurophysiologic foundation, the clinical use of tranquilizing agents in the geriatric patient is built. Many of the so-called psychologic phenomena observed in the geriatric patient seem to occur as he struggles to maintain

his previous level of attention and concentration against a gradually rising tide of mental inhibition determined organically. The psychologic manifestations of the geriatric syndrome are aggravated by the use of sedatives. With the use of tranquilizing agents, however, these manifestations are minimized. When the patient is more aware of his environment, he is better able to handle the problems which it presents.

There are certain dangers which must not be overlooked. In the elderly patient, particularly if there is advanced vascular damage, one of the great dangers is that of thrombus formation. Many believe that this is much more significant in the production of organic damage than hemorrhage or apoplexy. Purely upon the basis of the number of cases observed in practice, it would seem that if we use agents which cause hypotension we run the risk of thrombus formation as a side-effect. For example, there is immediate danger of thrombus formation in a patient whose systolic pressure of 180 has suddenly been reduced to 120—a response that may well occur in a patient who is in a state of decreased physical activity. This is, unfortunately, a complication that is all too frequent, as known to those who have worked in this field.

I have mentioned the complication, or danger, of incoordination, which results from loss of the righting reflex. The condition is of sufficient significance to warrant re-emphasis. The elderly patient rises from his chair and is unable to restore balance for a few seconds. We have had the unfortunate experience of observing the falls of other doctors' patients, and realize that it could very well have been our own patients who thus incurred a fracture of the hip.

Another aspect of over-tranquilizing the geriatric patient is the possibility of the development of various stasis phenomena, with peripheral venous thrombi. Upon occasion, there is a breakdown of the nutrition of the skin, particularly of the lower extremities. We have seen this condition once.

The masking of underlying processes is not properly a complication, but it should be borne in mind. This has been mentioned by Dr. Schiele. It is a complication that has arisen to embarrass me; I am sure it has not happened to you. The geriatric patient may, when adequately tranquilized, no longer be aware of disturbing stimuli which arise from underlying disease processes. Thus, we may cease to be aware of the possibility of other complications. Complete masking of the progression of such a disorder may persist until the clinical state is beyond reversal. Like Dr. Schiele, we have noted subdural hematomata in elderly patients whose gastric mucosa showed abnormalities of absorption, whose general vitamin intake was often lower than the optimum, and whose hormonal balance was below our usual concept of the normal range. Such states invite hemorrhage with minimal shifting of calvarium contents. Undoubtedly, many patients in chronic hospitals have died of undiagnosed subdural hematomata. This was true before the use of tranquilizing agents, and I am certain that it is equally true since their introduction.

Some rare blood dyscrasias may occur. We cannot administer these tranquilizing drugs, or any others, without watching for their effects upon the body as a whole. We speak of sensitivity reactions, but these differ from patient to

patient. It is often a matter of good clinical judgment to know when to discontinue and when to continue the use of these agents.

With ambulatory private patients, we have obtained somewhat better results by using a combination of tranquilizing agents. First, there is a careful and complete study of the patient; we must be certain that there is no masked condition such as a space-taking lesion of the brain. Then we proceed with a program of therapy based upon the concept that we are trying to block certain ganglionic connections. Geriatric patients are both more rewarding and more difficult than younger, more standardized patients. We usually start (when we are sure that the patient has the characteristic syndrome of the geriatric age group) with chlorpromazine in a dosage of 25 mg. four times daily (after each meal and at bedtime). To that, we add reserpine—0.25 mg. four times daily, given at the same times. Because these drugs have a hypotensive effect, amphetamine is also given, usually in the morning and at noon; at times it is given three or even four times a day—5 mg. in the morning, 5 mg. at noon, and 2.5 mg. in the afternoon or evening. Oddly, this has not kept the patients awake but has appeared to assist in compensating for the hypotensive and depressive effects of the tranquilizing agents. In severe agitation, it has been necessary to use relatively larger doses of tranquilizing drugs and, to obtain control, we have had to use intramuscular injections, particularly early in tratment. In these instances, treatment is not on an outpatient basis. Dr. Kline, I am sure, will talk about ways of securing complete control rapidly. We have followed his recommendations and find them to be quite satisfactory.

We have observed one of our colleagues using chlorpromazine intravenously. This is not without danger. We would be disinclined to recommend it generally, but it has served a valuable purpose in some cases. Because of the problem of buffering to achieve the proper pH for the injected material, we would advise against the general use of the preparation in this manner.

In the management of geriatric patients, we have found tranquilizing agents to be of distinct value and assistance in handling what has previously been a most difficult clinical problem. We would emphasize that none of the tranquilizing drugs is without side-effects. All of them act primarily as ganglionic-blocking agents. By using a combination of tranquilizing drugs to obtain the desired action, patients may be kept more calm and comfortable and treatment will be more effective. The last is the objective of therapy in the geriatric patient. If we are able to restore him to some degree of effectiveness, he ceases to be a patient in the usual sense of the word. He is able to be out of the hospital and to engage in some type of activity. Obviously, in private practice, our concern is to keep the patient occupied. If I were to have a motto for people in the geriatric age group, it would be: "Don't retire. Change what you do, but don't retire." I can think of nothing worse than to repeat Lilly's experiment of removing the organism from all incoming stimuli and insulating it completely. Under these circumstances, one observes the disintegration of the organism as a whole and of the central nervous system specifically. I prefer to think of tranquilizing agents as reversing Lilly's experiment. These drugs break the insulation, as it were, and

allow the patient to become aware of his environment and to be effective. In this manner they are of distinct help in treating geriatric patients.

MODERATOR AYD: Thank you, Dr. Parsons.

Dr. Douglas Goldman will tell us of his vast experience in treating patients, both on an ambulatory basis and in a state hospital. Dr. Goldman.

DR. DOUGLAS GOLDMAN: Reference has been made to a number of aspects of the treatment of patients with tranquilizing drugs, and these should be emphasized. The physiologic effects of such drugs, when used therapeutically, present a few stumbling blocks in the way of complications. Therefore, a discussion of some of these complications is pertinent at this point.

The phenothiazine drugs and reserpine can produce parkinsonism 1) if the patient be susceptible, 2) if the dose be large enough, and 3) if the medication be continued long enough. This type of parkinsonism, however, is amenable to control. It should be detected and treated early, and should not be allowed to become so severe that the patient is "frozen." The first step in treatment is regulation of the dosage of the tranquilizing drug, and the addition of anti-parkinsonism agents. In our experience, Cogentin probably has produced the most favorable results, but Kemadrin and Pagitane have also been very effective. Belladonna derivatives seem to be less useful in the treatment of drug-produced parkinsonism. It makes little difference whether reserpine, chlorpromazine, or one of the newer phenothiazines has produced the parkinsonism; the management is the same.

The other large group of complications comprises skin reactions. These are most prominent with the use of chlorpromazine, but occur occasionally during administration of other drugs. They take the form of allergic-like reactions and respond to the use of antihistamines. Severe cases require adjustment of dosage of the tranquilizing drug, or even withholding of it for several days.

Among antihistamines, we have no favorites. Any of the good ones seems to work. In the most severe cases, we use moderate doses of adrenocorticotropic hormone in addition. Usually, the slow-acting form of ACTH (the gel, or the zinc compound) seems to be effective in relatively small amounts when given for a week or less.

Jaundice, which has plagued the use of chlorpromazine, recently seems to have been occurring less frequently. In our experience, it has always been benign. It subsides within a few days, particularly when recovery of function is accelerated by use of a small amount of adrenocorticotropic hormone, such as 10 or 20 units of the slow-acting form every other day. After jaundice has subsided, we usually resume chlorpromazine, with longer intervals between increments in dosage. Thus a number of our patients who had jaundice initially could be treated eventually with very large dosages (800 mg. or more a day).

The most frightening complication is agranulocytosis, which may occur during administration of chlorpromazine and of other phenothiazine derivatives in similar or greater dosage. When recognized early, it is not as dangerous as its old reputation would indicate. Immediate withdrawal of the drug and the frequent use of large amounts of antibiotic (usually a combination of two or more,

as the associated infection is likely to be a symbiotic one) will protect the patient against further loss of polymorphonuclear leukocytes sufficiently long for regeneration to take place. We believe that regeneration can be accelerated by the use of adrenocorticotropic hormone, but this belief is not universally held, and we respect other people's opinions.

Careless injection of chlorpromazine can cause a necrotic area in the buttock, which may take several weeks to heal. In injecting chlorpromazine, it is necessary to dilute the material in the ampul with an equal part of physiologic salt solution, and to add hyaluronidase to accelerate absorption.

Some elderly patients will not swallow the pills, but let them disintegrate in the mouth over a long period of time, causing irritation of the mucous membranes. Therefore, if chlorpromazine is to be given to such patients by mouth, it should not be in concentrated form.

Cheilosis, characteristic of riboflavin deficiency, may result from the long-term use of a phenothiazine drug, chlorpromazine or reserpine, particularly when the dosage of the latter is pushed to a fairly high level and produces some drying of secretions. The cheilosis clears promptly with the use of 10 mg. of riboflavin three times a day.

Dermatitis of the contact type associated with riboflavin deficiency in an elderly person may be cleared by the use of riboflavin, antihistamine, and ACTH.

A kind of contact dermatitis may at times be associated with the use of reserpine. It may be relieved by administration of antihistamine and ACTH and prohibition of the use of any detergent (which apparently is the triggering agent in many of these dermatitides).

Torticollis is another complication of extrapyramidal origin which may be observed during therapy with chlorpromazine.

Necrotic spots on the tongue may be associated with agranulocytosis, or there may be a large necrotic area in the throat. I have seen one on the skin of the hand.

We might mention a number of other things. It was said that destruction of brain cells would preclude the usefulness of the tranquilizing drugs. In many organic conditions (including pareses) which occur in older persons, there is inadequacy of brain tissue, but the usefulness of these drugs in helping to make such patients socially acceptable does not seem to be diminished. In the treatment of delirium, such as that associated with alcohol, these drugs have a distinct place.

I should like to second Dr. Parsons' comment on the occurrence of thrombosis, particularly, and perhaps only, when the tranquilizing drug is pushed. This applies, for instance, to chlorpromazine and reserpine given rapidly and in doses so large as to produce hypotension. Patients cannot tolerate such administration nearly so readily as they can doses slowly increased to the level of usefulness.

Subdural hematomas in carefully run state hospitals are not so frequently neglected as may sometimes be supposed. This is defensive on my part, and I recognize it as such.

I must add a word of caution about the intravenous use of chlorpromazine.

Intravenous injection can often be accomplished with impunity, but occasionally there is a shock-like reaction which requires the use of norepinephrine over a considerable period of time, for recovery. This reaction has occurred to the consternation of a number of experimenting scientists who used the material on themselves.

There are many elderly patients, both in private practice and in state hospitals, whose conduct can be made socially acceptable through the use of chlorpromazine. Thus they can be cared for at home rather than in institutional settings, or can be kept in better institutional settings—in nursing homes rather than in state hospitals. In one of the nursing homes that I visit once a month, the nurses claim that since the introduction of the tranquilizing drugs the old patients have been much easier to handle, their appetites have been better, and they have not been so destructive nor nearly so frequently incontinent.

MODERATOR AYD: Thank you, Dr. Goldman. We shall now call upon Dr. Nathan Kline.

DR. NATHAN S. KLINE: First of all, it is worth pointing out that in one sense the pharmaceutical industry has brought about one of the major problems in psychiatry today. It is precisely the problem we are discussing. For example, because of lives saved by the introduction of various antibiotics, our hospital population has increased. In the New York State system in the past twenty years, the percentage of patients with arteriosclerosis and senile psychosis has increased from less than 20 per cent to more than 30 per cent—directly attributable to the prolongation of life.

In addition to the pharmaceutical industry, other people are responsible. The sociologic structure of our society is such that it has become an increasing problem to find someone to stay at home to look after Grandma. If she leaves the gas on or flushes $20 bills down the toilet, we now relegate her (because of small living quarters, and several people in the family working outside the home) to a state hospital. As Dr. Goldman has indicated, something other than state hospitals and custodial nursing homes is needed. I am afraid, though, that I cannot offer a solution.

Incidentally, the same is true of the Veterans' Administration. Unless we have another war, it is going to become a geriatric service in the not too distant future. This certainly is a pressing problem.

As for psychologic factors, some good studies have been made, particularly a recent review by Dr. Busse of Duke University who is interested in the problem. He compared successful oldsters with those in state hospitals. He pointed out certain social factors that seemed to differentiate the successful from the unsuccessful. Prominent among such social and psychologic elements favoring good adaptation to old age was the experience of being needed. He found that persons who could contribute in some way to the family were much more successful than those relegated to the shelf. Even being able to give a little help to grandchildren meant a great deal to the old person. Busse differentiated such "contributors" from nonparticipant "observers." He also pointed out that persons who were slightly selfish—self-thinking—seemed to live longer than those who devoted themselves entirely to other people.

It is well known that an active sexual life is correlated with longevity. What is cause, and what is effect, is hard to say. In some recent experiments, senile rats were divided into control and experimental groups. In the experimental group, young females were put with old males. The longevity of this group was significantly greater than that of the "stag" colony. I don't know whether this can be popularized as a method of treatment. However, if anyone objects, it should be pointed out that there is good historical precedent. The Bible (Kings I) refers to David "old and stricken in years" who took unto himself Abishag, a young virgin. (It must be added that "the king knew her not.") Apparently, this is not a new method of handling the problem.

The use of reserpine and chlorpromazine in calming excited, agitated, elderly patients is well known. Other phenothiazines such as Compazine, Sparine, and Pacatal are also useful (particularly the last, if there is mild depression) but careful watch should be kept in order to detect possible blood dyscrasias and jaundice at an early stage. Good hydration seems to offer some protection. The most potent of the newer preparations, on a milligram-for-milligram basis, is Trilafon. This product, along with Compazine, Vesprin and reserpine, offers the advantage that it does not tend to produce agranulocytosis. I agree that in some cases a stimulant is also indicated. In addition to amphetamine compounds, we have found Ritalin quite useful.

Another drug which has been advocated is Metrazol. We are presently working with a compound, 10-10-4, which consists of Metrazol, nicotinic acid, and reserpine in combination. Our study has not progressed far enough, however, to say exactly how good it is. I have reviewed the literature in detail and found that no one has carried out a large-scale study to determine the usefulness of Metrazol. The most recent report was in April of this year by Linden, Courtney, and Howland. They performed a good experiment, with controls. The control patients received thiamine and ascorbic acid, and the experimental group received Metrazol plus thiamine and ascorbic acid. Hemoglobin levels tended to improve in the experimental group. Nine patients in the experimental group were released from the hospital as compared with 3 control patients. Ten were much improved as compared with 3 control patients, and so on—the control group tending to show no improvement. Thus, this drug should certainly be considered.

In using the newer medications, one should not forget such standbys as vitamins. Dr. Goldman has pointed out how they tend to become involved. One commercial preparation—Neobon—contains lysine in addition to an extensive assortment of vitamins and minerals. In several cases it has proved surprisingly successful.

A good night's sleep is among the most important therapeutic measures, since many of these patients fall into a vicious cycle of daytime fatigue and drowsiness with nocturnal restlessness. Therefore, a good sleep-producing preparation is extremely important in handling such cases. When nocturnal restlessness is exaggerated, many of these persons become night-wanderers, which is often the direct cause of a need for hospitalization. We have conducted fairly extensive experiments in an attempt to find good sedatives. The best to date has been

trichloroethanol (ET-395) which, in an experimental group, was able to provide night-time sedation without hang-over the next day, as usually occurs with barbiturates. Doriden, Miltown, Equanil, Valmid and Phenergan, among others, have also been useful in selected cases.

One avenue of basic approach which we are just beginning to explore is derived from the work of Marmorston, which suggests that certain hormones can produce revascularization. It is too early to provide any definitive statement but, if successful, this work may introduce a new area of therapy. Actually, the probability of improved technics for the treatment of geriatric patients is extremely good. As the problem continues to become more intense because of increasing incidence, more and more effort will be devoted to it.

MODERATOR AYD: Thank you, Dr. Kline.

As a private practitioner of psychiatry who has had experience with most tranquilizers, I should like to take the liberty of expressing a few thoughts on this subject.

Physicians who treat patients with tranquilizers must consider the nature of the illness, its severity and its duration before prescribing a drug. Thus, a comprehensive behavioral history is essential for the selection of suitable candidates for specific drug therapy. While taking the history the physician should determine whether or not the patient has previously taken a tranquilizer and what his response to it has been. Such information enables the physician to prescribe wisely by avoiding drugs unsuitable for the patient. This, of course, assumes that the physician is familiar with the drugs he uses. Such knowledge can readily be gained by learning as much as possible about one or two drugs rather than learning a few superficial things about all tranquilizers.

When prescribing these compounds for ambulatory patients, it is always wise to commence with small doses and to increase as rapidly as necessary. By small doses, I do not mean homeopathic doses. It is ridiculous to prescribe 10 mg. of chlorpromazine as the starting dose for most patients. The initial dosage should be adequate, and then increased until a therapeutic level is reached. Once this has been achieved, however, the drug should not be discontinued immediately. Rather, the dosage should be reduced gradually over a period of weeks or months. Too rapid withdrawal sometimes can lead to physiologic disturbances, but most often leads to a relapse. Instead of blaming the drug, the physician should ask what is wrong with the way the particular compound is used.

In elderly patients, the initial dosage of chlorpromazine may be 25 mg. two or three times daily, followed by gradual increases. Some patients may need 200 or 300 mg. or more daily, even on an ambulatory basis. This is safe, if you have watched your patient and have increased the dosage gradually.

When using a drug with a potential for producing certain side-effects, it is good medicine to tell the patient and the family, if possible, what may happen. They should be asked to notify you of any sudden change in the patient's clinical or physical condition. In that way, serious side-effects such as agranulocytosis can be detected early. As Dr. Goldman pointed out, prompt detection and treatment of such conditions assure good recovery.

Dr. Goldman mentioned jaundice, and the fact that it is frequently benign. I believe that jaundice is an allergic phenomenon. We have found that, even if we do not stop the activating drug, the jaundice clears. However, as a rule of treatment, if a patient has jaundice the drug should be stopped. After jaundice has cleared, the treatment can be resumed, if necessary. Rarely, a second attack of jaundice develops, but I have never seen a third attack. Tranquilizing therapy can be resumed after the second attack has cleared.

Hypotension is a genuine problem in the geriatric patient. Dr. Parsons alluded to the danger of falls and hip fractures. This raises a question about the intramuscular administration of a tranquilizing compound (whether it be a phenothiazine derivative or a reserpine product) in the office. We know of a patient who had been taking chlorpromazine for two years, and received it routinely from her family physician by intramuscular injection at least twice a week. This went on for a long time in perfect safety. Following an intramuscular injection one evening, the physician dismissed her immediately instead of having her rest in the office for a while. While crossing the street, she experienced a hypotensive collapse in the path of an oncoming car. It was fortunate that she was not killed.

The administration of barbiturates in conjunction with ataractic drugs deserves mention. The question of possible potentiation of the action of barbiturates arises. This occurs only in the initial stages of therapy. The longer the patient takes the drug, the less likely is there to be potentiation of barbiturates.

Dr. Kline mentioned ET-395. We have had similar experience with it. It is a fine sedative. He did not mention its unpleasant taste. In order to get ambulatory patients to take it, the taste must be masked.

All of the new tranquilizing drugs represent an advance over barbiturates, bromides and chloral hydrate. However, they are really not the final answer to the troublesome emotional problems of everyday practice, and a need for new drugs exists. For that reason, I should like to tell you about a new compound called Trilafon. It is a tranquilizer, rapidly active and therapeutically effective with a minimum of side-effects. It calms excited, agitated and anxious patients, but has no effect upon depressions. It is a very potent drug, which is rapidly absorbed. Small doses are usually therapeutic. There are many advantages, in that the physiologic and neurologic responses to it are minimal, and thus side-effects are avoided.

I have some notes on this drug and should like to tell you what we have experienced. Because of its pharmacologic properties, we thought that Trilafon might be helpful in the geriatric patient. After a study with 200 patients, we selected 25 between the ages of 60 and 80 years. Typical diagnoses were severe neurotic reaction or paranoid reaction. Actually, the diagnosis played a minor role in the selection of patients for treatment. We chose them primarily because anxiety, agitation or excitement was the predominant symptom. The moderately disturbed patients received initially 4 mg. of Trilafon twice daily. Any additional necessary tranquilization was achieved through increasing the dosage by increments of 4 mg. until a therapeutic level was reached. For most patients, 12 to

24 mg. of Trilafon per day proved sufficient. We gradually discontinued it over a period of months in the same way that we would discontinue chlorpromazine or any other drug. As with other tranquilizers, if we reduced the dosage too rapidly, there was a tendency towards relapse. A few of these patients apparently will require maintenance therapy.

Treatment was initiated in disturbed patients by giving the drug orally or intramuscularly. (Trilafon causes no pain upon intramuscular injection.) We have also given it intravenously, but I do not advise this route in an outpatient, as Trilafon is an extremely potent compound.

Disturbed patients received initially 8 to 16 mg. of Trilafon a day orally. When we used the drug intramuscularly, we started with 5 or 10 mg. at eight-hour intervals. This quickly produced a quiescent state characterized by sleep. After three or four painless intramuscular injections, it was possible to change to oral medication. Thereafter, the dosage could be adjusted and gradually discontinued.

Trilafon is not a powerful hypnotic. It is a powerful tranquilizer. It does not produce drowsiness or lethargy, such as we have observed with other compounds, unless given in larger doses than are necessary therapeutically in most patients. As it is not a potent hypnotic, we use barbiturates in conjunction with it whenever insomnia is severe. This combined therapy is safe and practical. Trilafon does not potentiate the action of barbiturates.

The most dramatic results were obtained in patients who were the most disturbed—which is exactly what we observed with the use of chlorpromazine or reserpine. Trilafon takes effect rapidly, so that after three to seven days most of the patients began to have at least subjective relief from anxiety, which was followed by behavioral changes proportionate to the affective changes.

When treating a psychotic patient at home, it is important to remember that Trilafon does not wipe out delusions, nor does it do away with hallucinations immediately. However, the patient does not verbalize them any more, because the delusions are not reinforced emotionally. If you ask him about them, he says he still has all his ideas, but that they no longer bother him. Sometimes the family is concerned because the patient still voices delusions and they think that he is no better. Actually he is. At least, he is not acting out his delusions.

Neurotic patients reported that their obsessions and phobias were still present, but that these no longer troubled them. The physical manifestations of disturbed autonomic function, so frequently associated with anxiety, were minimized or eradicated in patients who were improved by this drug.

Trilafon does not affect depressions. However, we gave it in conjunction with electroshock therapy, as it eliminates any associated agitation.

Trilafon apparently is also a potent anti-emetic. In 2 patients with terminal carcinoma, who had severe nausea and vomiting, it abolished these symptoms almost immediately, and there was no recurrence during continued administration. Of the 200 patients in this study, some were pregnant. In them, nausea and vomiting and the morning sickness of pregnancy were eradicated by this compound.

Trilafon produces side-effects. Like other tranquilizers, it causes some weakness and fatigue, but they are not as marked. They can be treated with Ritalin, which is an excellent drug for counteracting lethargy and fatigue, whether produced by tranquilizer, by antihistaminics, or by anticonvulsants. Most of the side-effects of Trilafon—aching arms and legs, occasional constipation, and increased dreaming—occur in the first few weeks of treatment and then seem to disappear spontaneously. The most frequent side-effects observed were extrapyramidal symptoms, such as restlessness, tremulousness, and parkinsonism. These symptoms can be relieved by altering the dose, or by adding an anti-parkinsonism drug. We found Cogentin good for this purpose.

Fortunately, anti-parkinsonism drugs and reduction of dosage, have not often been necessary, because the symptoms usually do not occur when patients are taking less than 20 mg. of Trilafon a day. In most moderately disturbed patients, 24 mg. a day is the maximum dosage. In patients who are more disturbed, the initial requirement is greater, but the dosage can be reduced shortly, so there is not much of a problem.

I should like to emphasize that the incidence of extrapyramidal symptoms with this drug is quite high in ambulatory patients. One should not wait until full-blown parkinsonism has developed before adding an anti-parkinsonism drug. Some of the first symptoms—muscular aches and pains, and the like—are really the initial symptoms of a developing parkinsonism. That is the time to add an anti-parkinsonism drug.

With advancing age, drug sensitivity and intolerance increase. Barbiturates, for example, may stimulate instead of sedate. The ensuing anxiety or restlessness may lead to the injudicious prescribing of more barbiturates. Reactions to the various compounds we are using today are more likely to occur in the aged. Although thus far we have not seen any cases of sensitivity or intolerance to Trilafon, it should be emphasized that this drug is a phenothiazine derivative. Moreover, because of the propensity of the geriatric patient to be drug-sensitive, physicians who use this compound (or, for that matter, any compound) must be alert for possible adverse reactions and be ready to institute counteracting measures immediately.

Psychiatry has made considerable progress in the last few years in many ways that could not be accomplished by this branch of medicine alone. We need the general practitioner, the man who sees these people at home. If he learns how to use tranquilizing drugs properly, undoubtedly many patients can be kept at home, or at least be taken care of for a while in a general hospital or nursing home, and thus cut down on the overcrowding of state hospitals.

I have one final comment about tranquilizing drug therapy. Try to evaluate the patient's environment while he is being treated, because the effect of environment upon the amount of drug that the patient will need is tremendous. For example, if a patient is placed in a private room in a general hospital and given 50 mg. of chlorpromazine intramuscularly, he will invariably go to sleep. If he is in a semi-private room, he may become drowsy. If he is in a ward, he will stay awake.

We have experienced the influence of environment on dosage numerous times. We have sometimes removed a patient from a home where there was considerable turmoil, rather than give him large doses. Another device is to give the relatives a little medication temporarily until the enviroment quiets down; then things can be worked out satisfactorily.

DR. SCHIELE: Dr. Ayd, may I make one comment about depression? The new drugs, remarkable and helpful though they are, do not afford much relief for the depressed patient. Depression is one of the most common illnesses with which we have to deal. Electroshock, with all its disadvantages, is still the most efficacious treatment. This is particularly true of the delusional type of depression.

This point needs emphasis, because, with all of the publicity and enthusiasm about the new drugs, we find a number of patients who object to electroshock therapy and beg for the new drugs instead. In an occasional patient, these drugs will provide relief from agitation and some lessening of depression, but, in my experience at least, they help most depressed patients only temporarily, if at all.

DR. KLINE: Dr. Goldman and I would like to submit one statement with respect to Trilafon, about which there is mild dissension by Dr. Ayd. Hallucinations and delusions in a large number of our patients *have* cleared. I am interested that you found that you were able to elicit them. We think that, if you continue treatment long enough, they will disappear.

I should like to add that Compazine, which was recently introduced, seems to have the same order of action as reserpine and chlorpromazine. As Trilafon has not yet been extensively tested, comparisons are difficult, but it is certainly a drug with extremely potent ataractic action.

DR. GOLDMAN: I agree. The more potent drugs like Trilafon and Compazine should be handled with great care because of the possibility of producing dystonia and parkinsonism at relatively low dosage levels.

We have seen parkinsonism develop during treatment with only 12 mg. of Trilafon a day and with only 30 mg. of Compazine a day. These cases, however, were mild and responded quickly to treatment—much more rapidly than the parkinsonism produced by larger doses of chlorpromazine. It is simply a question of not allowing this effect to get out of hand. That is the important thing.

MODERATOR AYD: Dr. Parsons?

DR. PARSONS: Dr. Ayd, in behalf of the patient who receives an intramuscular injection of chlorpromazine, I would suggest that, in addition to what Dr. Goldman mentioned, 1 cc. of procaine, or a similar substance, be added. Chlorpromazine is highly alkaline and its injection is painful. It is far better to decrease the pain. The patient is more comfortable, and you are relieved when he does not return with a sore muscle.

MODERATOR AYD: Are there any questions from the floor?

SPEAKER: What was the drug referred to with respect to night-wandering?

MODERATOR AYD: Dr. Kline, please?

DR. KLINE: The drug is trichloroethanol. It is not yet on the market; but,

so far, it has been the most successful drug tht we have used for this purpose. Incidentally, it is a good sedative as well. Its action is particularly good in patients who have difficulty in going to sleep. The patient can waken in four or five hours and feel completely refreshed. He has a feeling of floating off to sleep rather than being "knocked out," as frequently happens with barbituarates.

DR. PARSONS: Dr. Kline also mentioned cherry brandy a few minutes ago. I don't know whether there is a relationship between the two or not.

DR. KLINE: Dr. Ayd was objecting to the taste of trichloroethanol, and I agree. It tastes like very bad cherry brandy—the first run off the mash. When he complained about the taste, the reference to "cherry brandy" was a spontaneous free association.

MODERATOR AYD: Are there any questions from the floor?

SPEAKER: I noted Dr. Goldman's remark about the too careless intramuscular injection of chlorpromazine, and that the intravenous preparation had to be used with a different technic. Is the action of promazine (Sparine) the same as that of chlorpromazine (Thorazine)? Does it have the same uses?

MODERATOR AYD: No. We must distinguish between the drugs. Promazine is a much milder drug than chlorpromazine. In our experience, it is less effective in controlling intense symptoms. In using chlorpromazine intravenously, the possibility of a hypotensive reaction must be kept in mind. There are also shock-like responses that require norepinephrine to help in recovery. As far as I know, there has been no such reaction to promazine.

SPEAKER: Hypotensive responses?

MODERATOR AYD: I mean from intravenous promazine. Hypotensive reactions can occur with oral and intramuscular promazine.

SPEAKER: Are they milder?

MODERATOR AYD: Yes. Any more questions?

SPEAKER: Is Phenergan of use in controlling side-effects?

MODERATOR AYD: Dr. Kline will answer this question about Phenergan.

DR. KLINE: We still have no way of knowing in advance which patients will respond best to Phenergan or one of the other drugs. It is largely a matter of trial and error with the compounds now on the market.[1] The same is true of adjunctive medications. I agree with the other speakers that Cogentin is generally the best. I believe that we were the first to point out its usefulness for this purpose (A. A. A. S. Meeting, Berkeley, California, 1954). In some patients the side-effects of ataractic drugs do not respond to Cogentin but do respond to Phenergan, and the same can be said of Doriden and certain other products. Incidentally, Phenergan is a good sedative. For a while, we thought that some of our good results might not be due to the so-called ataractic drugs, but to Phenergan. We conducted a separate experiment with it and found that it was a good

[1] Since the time of this meeting, we have presented our work with iproniazid (Marsilid)—an energizer rather than a stimulant—which appears to have extensive application in the field of geriatrics. (*Cf.* Present Status of Psychopharmacological Research—Including Iproniazid, by H. Loomer, J. Saunders, and N. Kline. Hearings before the Subcommittee of the Committee on Appropriations. United States Senate, Eighty-Fifth Congress, First Session on H. R. 6287, pages 1344–1390, May, 1957.)

sedative but that it did not have so-called ataractic properties. I also agree with Dr. Schiele that electroshock is still indicated in depressions,[2] even though we have recently reported on the use of Thorazine and Phenergan in combination, which appears to provide some relief from depression. Pacatal has also proved useful in mild cases.

DR. GOLDMAN: It is important to understand that Cogentin is a specific for parkinsonism and has relatively little sedative action. We have occasionally used Benadryl to overcome allergic responses to drugs, and have found it to be a very good sedative in patients such as ours, as it is in other people. It readily produces sleep.

MODERATOR AYD: Are there any more questions?

SPEAKER: Will you please comment on the hypotensive effect of Trilafon. Have you seen any skin reactions with it?

MODERATOR AYD: Thus far, we have observed no skin reactions nor any hypotensive responses. It does not seem to have that particular property.

SPEAKER: Claims are made that, in geriatric patients, Glucovite relieves nervousness and cerebral disorders when loss of memory is involved. Has this drug any value?

MODERATOR AYD: Dr. Parsons will answer your question.

DR. PARSONS: The use of this drug is based upon the concept that, if you furnish adequate food to the brain, it will function better. It is something like "taking a horse to water." We have observed no benefit from this particular, highly publicized preparation. Our experience was the same in the use of the preparation in the treatment of feeblemindedness. When these substances come in contact with gastric juice, the hydrochloride is formed, which is the same compound that would be present anyway. We have not been able to demonstrate in the laboratory any beneficial effects from these various so-called food substances, and we see no advantage whatsoever in their use.

[2] Since our introduction of Marsilid for this purpose, we no longer think that electroshock is the method of choice.

TESTOSTERONE PELLET IMPLANTS FOR ADVANCED BREAST CARCINOMATOSIS IN THE FEMALE. PRELIMINARY REPORT*

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Despite great advances in early detection, prompt and radical surgery, and improved radiation therapy, mortality and morbidity remain high for patients with carcinoma of the breast. Although 5-year survival figures vary from one report to another, it seems safe to state that in over 50 per cent of cases there is recurrence or metastatic spread within the conventional 5-year period.

Since breast tissue is known to be responsive to hormonal stimulation, many attempts have been made to influence the clinical course of mammary carcinoma by altering the endocrine status of the body. Bilateral ovariectomy, adrenalectomy and hypophysectomy as surgical techniques, and the administration of androgens, estrogens, cortisone and other hormones or related products have met with some degree of success, as judged by the many available reports.

In this preliminary report we wish to present some of the observations made within the last ten years upon a group of 100 women treated by subcutaneous implants of testosterone pellets for palliation of advanced and otherwise intractable breast cancer.

CLINICAL MATERIAL AND METHODS

All of these 100 women were patients for whom conventional therapy had nothing further to offer. In most cases surgery and extensive radiotherapy had been followed by local or metastatic recurrence; in the others, the diagnosis had been made only after extensive spread of the disease had already occurred. About a third of the patients were bedridden and victims of excruciating pain; many had open ulcerated tumor masses; and some had had spontaneous fractures. All possible locations for metastases were represented.

Androgenic therapy was administered to all patients in whom the disease had its onset less than ten years after the menopause. Older patients were treated by oral administration of large doses of synthetic estrogens. Cortisone therapy was added in some cases at late stages.

Treatment usually started with the implantation of 750 mg. of pure crystalline synthetic testosterone in the form of 10 cylindrical compressed pellets of 75 mg. each. The implantation was carried out as follows: After local anesthesia, a small incision is made in the skin of the selected area (usually the abdominal wall) in

* Presented by invitation at the "II International Symposium on Mammary Cancer," University of Perugia, Italy, July 23–31, 1957.

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order to insert the special trocar[1] through which the pellets are pushed into the subcutaneous fat. The trocar is removed and the edges of the small incision are held together with a small strip of adhesive plastic tape. There is rarely any bleeding and the incision heals within two to three days. With careful handling, there is neither pain nor inflammatory reaction. The pellets remain palpable for several months at the site, gradually decreasing in size. As the purpose was to produce the maximum possible absorption of testosterone in order to study its effects at massive levels, the implants were repeated at weekly intervals until maximum therapeutic benefits were observed. Attempts were made to determine for each patient how much the intervals between follow-up implants could be prolonged without a loss of therapeutic benefits. Usually the implants were given weekly for six to twelve weeks, then at increasing intervals of two, three and four weeks for the next year or two. In the cases maintaining a satisfactory state of remission or apparent arrest of the neoplastic activity, the times of implantation were spaced farther apart on successive years of treatment. One patient has completed eight years of apparent complete remission. For the last two years the implants have been given at six-month intervals—the longest intervals we have tried so far. Other patients are still receiving implants at intervals of two, three and four months.

It was during attempts at prolonging the intervals between implants that we observed the most frequent reactivations of the neoplastic process. At such times, a quick intensification of therapy with three or four implants a week apart usually induced a new response; maintenance therapy was then given at shorter intervals than previously.

RESULTS

We are not attempting an evaluation of our results at this time. There are so many factors which vitiate the interpretation of data in a disease as protean as cancer that we shall not risk adding to the present confusion with our relatively small series. Our purpose is simply the presentation of some of our most frequent findings. It must be emphasized that results have been mostly temporary and palliative, although in some cases they have been impressive in intensity and duration.

We considered as positive responses to therapy only those involving significant alleviation of pain, return of appetite, gain in weight and strength to the point of ambulation, and the ability to undertake moderate physical activity for a period of at least eight weeks after the beginning of treatment. On the basis of these criteria alone, and not considering objective changes in the lesions themselves (such as reduction in size of tumor masses, healing of ulcers or calcification in bone metastases), the responses were satisfactory in over 90 per cent of the patients. On the basis of objective evidence alone, our results were no better or worse than those previously reported by investigators who used the more conventional intramuscular injections of testosterone propionate in oil, or the newer synthetic derivatives now on trial. However, the implants are needed

[1] Kearn's pellet implanter.

much less frequently than the intramuscular injections and cause far fewer local indurations and other tissue reactions. The much higher systemic concentrations of the hormone obtained from the implants seem to produce metabolic effects which are different. For instance, edema, hypercalcemia and undesirable masculinizing changes such as hirsutism, acne, enlargement of the clitoris and increased libido, although reported as frequent findings with conventional androgenic therapy techniques, were less frequent and less intense in our series.

Hirsutism was observed in brunettes who were already somewhat hirsute but it progressed slowly. Most of the blondes in whom hirsutism was observed had been receiving smaller doses of androgen and were already hirsute when referred to us. In at least 1 case the hirsutism decreased noticeably when therapy was changed to the more intense pellet-implant form. In other cases we observed that hirsutism made its appearance only when the intervals between implants were prolonged beyond two or three months.

Acne was not a problem in our series; only mild and rare instances were observed. Enlargement of the clitoris occurred rarely, and only early in the course of treatment as a transient period of engorgement with enhanced libido, not intense enough to require sedation. Edema appeared inconstantly and was never hard to control by means of moderate salt restriction in the diet, and occasional oral or parenteral (rarely) diuretic drugs.

Hypercalcemia was not observed in any patient in our group, but in 2 cases there was muscular cramping, with normal serum levels of calcium, inorganic phosphorus, alkaline and acid phosphatases and proteins. In 1 of these patients, still under observation, parenteral administration of calcium gluconate and oral intake of calcium salts and vitamin D seemed to be effective in reducing the intense and painful muscular spasticity.

The most impressive response has been the reduction or even suppression of pain, along with the production of a state of relative euphoria, increased appetite, gain in weight and strength, and a return for several months to ambulatory activities in patients referred as bedridden cases. The average duration of this type of remission was twenty-eight months.

ILLUSTRATIVE CASE REPORTS

Case No. 1. A 47-year-old Negress was admitted on June 1, 1952 because of progressive excruciating back pains. She had not sought medical help despite great suffering for several months. A large tumor mass occupied the right breast (Fig. 1-A). Ulceration underneath the breast extended to the middle anterior chest wall. Extensive metastases involved her spine and pelvic bones. The pain was so severe that large doses of narcotic drugs afforded no relief. Testosterone propionate was administered in doses of 200 mg. in oil intramuscularly every six hours and reduction in pain was observed within forty-eight hours. Within five days she was able to get out of bed after receiving the first pellet implant, and was discharged for out-patient follow-up. She required minimal amounts of analgesics—usually only aspirin thereafter—despite the many destructive bone lesions. She received weekly implants for a total of 6, and every two weeks thereafter. Four months later the breast tumor had decreased substantially in size, the ulcerations had healed and she was feeling well enough to return to work as a laundress (Fig. 1-B). Despite this external response and the marked subjective improvement, the bony metastases showed little significant recalcifi-

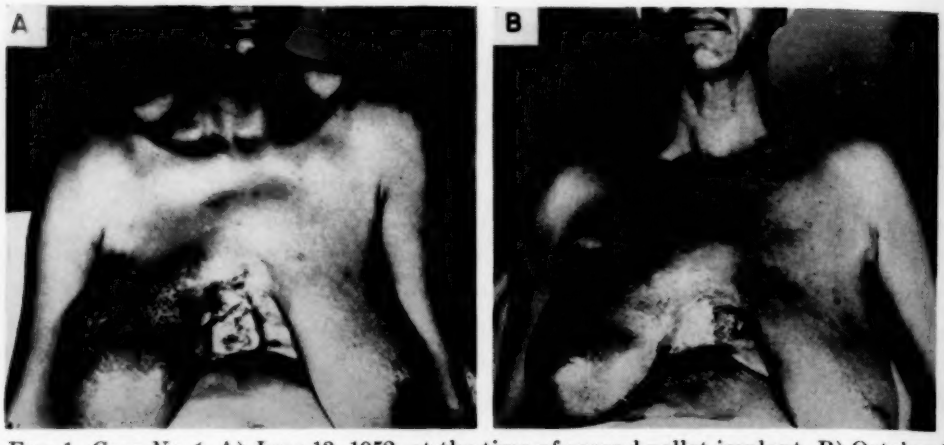

FIG. 1. *Case No. 1.* A) June 13, 1952, at the time of second pellet implant. B) October 17, 1952, after 12 implants (total, 9.0 Gm. of testosterone). Tumor mass is smaller; ulcerations have healed.

cation, though apparently the process remained arrested. She was feeling so well that she insisted on moving away to live with a relative in another state and has not been heard of again.

Case No. 2. Mrs. V. S. was a white housewife, born August 25, 1907. In May 1949 her right breast presented a hard tumor mass about the size of a baseball under the area of the nipple toward the right upper quadrant. There was "peau d'orange" and retraction of the nipple. Large lymph-node masses were felt along the outer border of the pectoral muscles and at the axilla. A biopsy report stated: "A rather mature scirrhous adenocarcinoma with marked desmoplastic reaction." Because of the large size and extension of the lesion, it was declared inoperable. While she received radiation (3000 R. units over a period of three months), pellets of testosterone were implanted once a week for six consecutive weeks and then gradually farther apart. At the present time, eight years later, she receives one implant every six months and has been doing so for the last two years. Each time she undergoes a thorough examination including an x-ray survey of the skeleton and lungs, and various pertinent laboratory investigations. An interesting feature is that three years after the initial biopsy was made, in view of the remarkable reduction in the gross size of the breast and axillary lesions, she volunteered for a mastectomy, which was performed April 4, 1952. The primary lesion was found to be of a size many times smaller than the initial one, but the histologic picture was identical with that of the original biopsy specimen and again was reported as "Scirrhous carcinoma with metastases to regional lymph glands and marked desmoplastic reaction in primary tumor." Despite the fact that no histologic changes were detectable, this woman is now (September 1957) in excellent health, with no evidence of neoplastic activity.

Case No. 3. A white female, born in 1891, was seen at the tumor clinic October 30, 1951, with a left mammary tumor of eighteen months' duration (Fig. 2-A). It was deeply ulcerated and smelt badly. There were multiple nodes on the skin of the trunk, axillae and neck. Biopsy (Fig. 3-A) revealed this picture: "The epidermis shows slight hyperkeratosis. There is intercellular edema in the stratum germinativum and flattening of the rete ridges. At one edge the epidermis is thinned and exhibits spongiosis and vesicle formation. The latter are often filled with an eosinophilic coagulum. In about 5% of the cells of the stratum germinativum sex chromatin is present. The dermis is edematous and is invaded by solid cords and nests of poorly differentiated cells, characterized by marked poly- and hyperchromasia, with distinct variation in size and a moderate number of mitoses per high-power field. Sex chromatin is observed in some of the tumor cells (Fig. 3-B). Diagnosis: Poorly differentiated solid carcinoma."

The patient was referred to our clinic for endocrine therapy and implants of testosterone

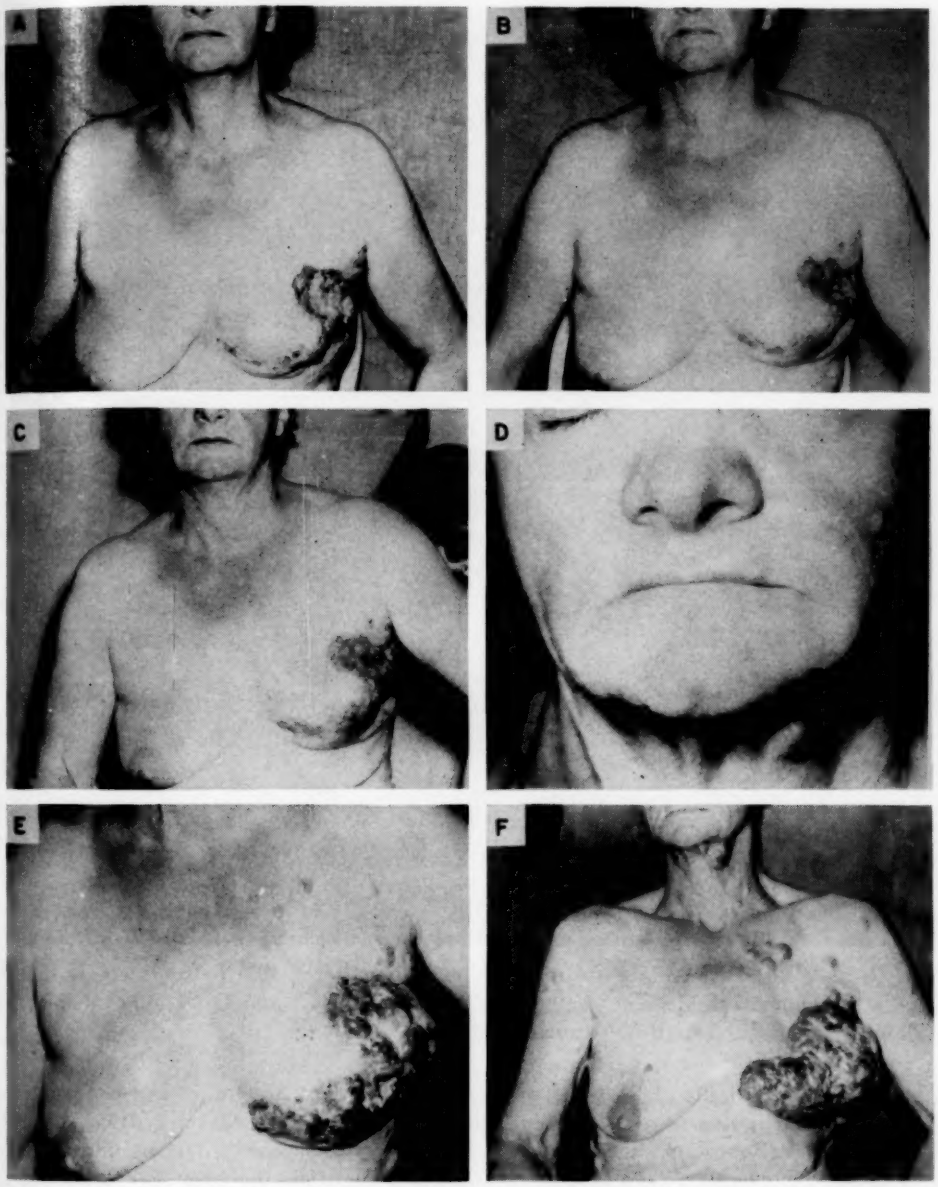

FIG. 2. *Case No. 3.* A) November 5, 1951, before testosterone implants. B) January 17, 1952, after 10 pellet-implants (7.5 Gm. of testosterone). C) March 27, 1952, after 4 more implants (total, 10.5 Gm.). D) December 13, 1952, after implants had been spaced two to three months apart; moderate hirsutism has appeared. E) Primary lesion again active, with great increase in cutaneous nodes. F) August 7, 1953, terminal stage of massive carcinomatosis. Hypophysectomy on this date was followed by softening and cyanosis of the cutaneous nodes, until death occurred from pulmonary embolism six days later.

were started on November 1, 1951. After only two weeks there was considerable regression of the tumor and the ulcerations became clean and covered by new epithelium. Implants were continued every two weeks and by December 20. 1951 "there was remarkable new epithelization of all ulcerated areas with distinct healing and shrinkage of all lesions." This improvement is recorded in the photograph (Fig. 2-B) taken January 17, 1952. After

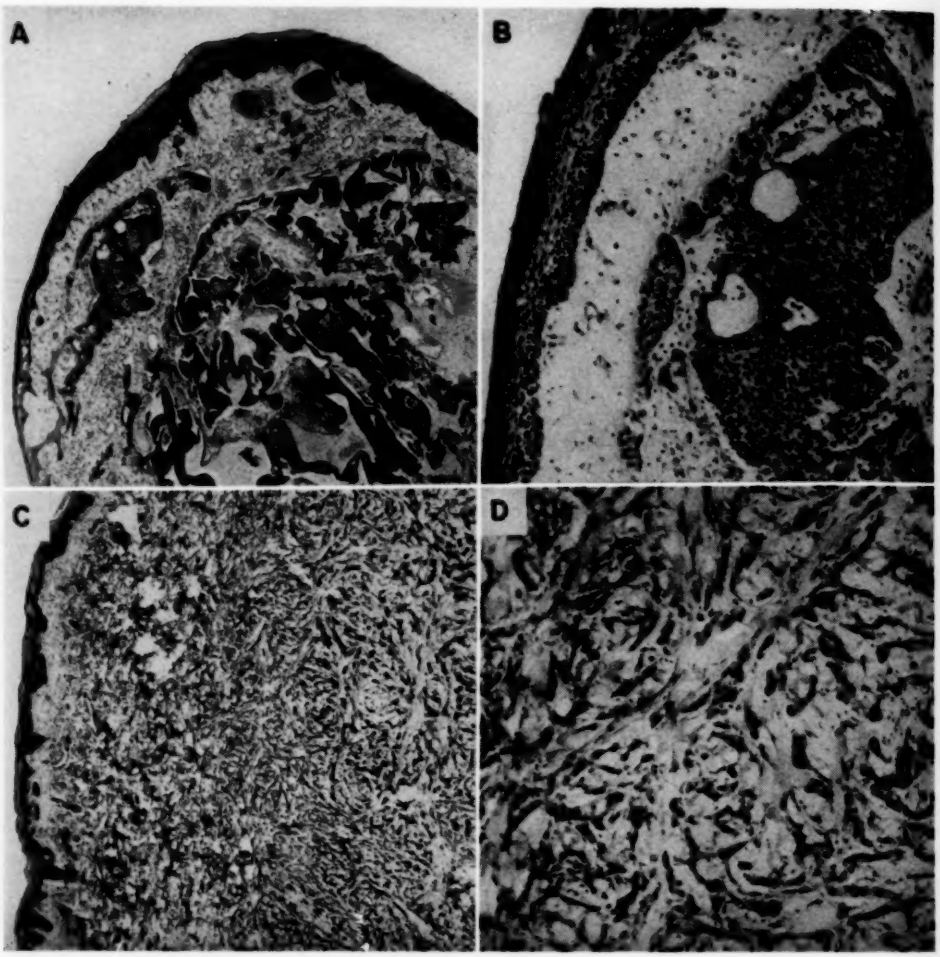

FIG. 3. *Case No. 3.* A) Biopsy of breast lesion, November 5, 1951 before testosterone implants. B) Higher magnification; segment of same section. C) and D) Second biopsy, June 17, 1952 (low-power and high-power magnifications). See text.

she had received implants of 100 pellets containing a total of 7.5 Gm. of testosterone there was no noticeable hirsutism and the lesions were still improving by March 27, 1952 (Fig. 2-C) while she was receiving implants at intervals of two to three weeks. After implants became less frequent (four to six weeks apart), not only did hirsutism increase (Fig. 2-D) but the primary lesion again became ulcerated and the nodules in the skin became more numerous (Fig. 2-E), pruriginous and partly ulcerated. Eventually the nodules were seen all over her skin (Fig. 2-F). Severe anemia also developed, requiring several blood transfusions. Implants of testosterone were stepped up again and a trial was made for a while with estrogen and with cortisone therapy. After two less intense remissions, her condition slowly deteriorated. A biopsy performed June 17, 1952, when the general clinical picture had not yet begun to deteriorate seriously (Fig. 3-C) showed the following picture: "In contrast with the first biopsy, the tumor cells are arranged in very small groups and slender cords, surrounded and compressed by dense strands of collagen and connective tissue, representing a well-marked desmoplastic reaction. The tumor cells show only rare mitoses, moderate pleomorphism and polychromasia, with evidence of rexis and piknosis. Sex chromatin is present in the epidermal cells as well as in some of the tumor cells" (Fig. 3-D).

She died of pulmonary embolism a week after hypophysectomy had been performed on August 7, 1953, the day the last photograph was taken (Fig. 2-F). At autopsy metastases were found mainly to skin, lungs, pleura and liver. Postmortem findings with reference to further effects of hypophysectomy in this patient have been described elsewhere (1).

In Table 1 are listed some of the laboratory data obtained during androgenic therapy in Case 3. These are representative of most other cases in this series, in that changes were slight and not always consistent with the clinical status, except for the occasional increase in the serum levels of alkaline and acid phosphatase when there was an intensification of neoplastic activity. Also observed was an increase in the serum protein-bound iodine level during the terminal stage of maximum tumoral activity and tissue destruction.

Thyrotoxicosis, with increased basal metabolic rate, thyroidal I^{131} uptake and serum protein-bound iodine concentration, was observed in several of our patients during "escape" from the therapeutic benefits of testosterone therapy. A "steroid type" of carbohydrate metabolic disorder with hyperglycemia and glycosuria, but rarely with clinical symptoms of diabetes, was also observed. Whenever an increase or a change in therapy induced a new remission, these findings subsided, in line with the general improvement and the rehealing of ulcerated lesions, reduction in size of the nodes, and recalcification of destructive bone metastases.

Every instance of recurrence was treated by intensification of androgenic therapy. In about half the cases, 2 more remissions were induced by 2 consecutive courses of testosterone implants several months apart; in a fourth of the cases, only 1 more remission was induced; and in the remaining fourth, there was no repetition of the initial remission.

TABLE 1

Laboratory Data on Blood Serum While a Patient with Breast Cancer Was Undergoing Treatment with Testosterone Implants

Case No. 3. Elizabeth F., born 1891; fungating mass in left breast and nodes in the skin

Date	Protein (Gm./100 cc.)	Ca (mg./100 cc.)	P (mg./100 cc.)	Phosphatase (Bodansky units)	
				Alk.	Acid
June 2, 1952.....		10.3	2.5	1.9	1.3
Oct. 11, 1952*...		9.2	2.9	8.2	2.3
Dec. 13, 1952....		8.9	3.4	1.5	1.4
May 22, 1953**..	4.8		4.2	3.6	1.3
May 25, 1953†...	5.2	8.9			
July 22, 1953‡...	5.9	10.0	3.9	2.6	1.7

* Extensive increase in skin metastases after implantation intervals reduced to two or three months. New remission followed more frequent implants.

** Severe anemia and frequent hemorrhages from primary tumor and some of the softened and ulcerated skin nodes when, after new remission, implants were again spaced two months apart.

† After blood transfusion.

‡ Near terminal stage: serum protein-bound iodine level had increased to 9.8 gamma per 100 cc. Stepped-up schedule implantation now had no effect.

SUMMARY

A preliminary report is presented of some of the clinical and pathologic observations made during a ten-year period in the course of treating 100 female patients who had extensive carcinomatosis originating in the breast. Testosterone (pure crystalline) compressed pellets (75 mg. each) were implanted, 10 at a time, into the subcutaneous fat through a special trocar. Implants were made at weekly intervals for six or more times. Then they were spaced farther apart—up to twice a year in a patient who survived for more than eight years, and three to six times a year in other patients who survived for periods ranging from three to six years.

Implants of pure testosterone have the advantage of more prolonged effect and less frequent administration than intramuscular injections of testosterone esters.

Masculinizing changes seemed to be less conspicuous than with other forms of less intense androgenic therapy. Edema was minimal and there was no hypercalcemia. In 2 cases tetanic muscular contractions were relieved by parenteral administration of calcium. As a rule serum levels of protein, calcium, phosphorus, and alkaline and acid phosphatase remained within normal limits. Exacerbations of neoplastic activity were accompanied occasionally by a transient increase in the serum levels of alkaline and acid phosphatase, and more frequently by an increase in serum protein-bound iodine concentration and thyroidal I^{131} uptake along with decreased glucose tolerance.

Subjective responses were good in over 90 per cent of the patients, as manifested by reduction or even suppression of severe pain, production of euphoria, and gain in appetite, weight and strength. The duration of remissions was variable, averaging twenty-eight months, with a range of eight weeks to more than eight years.

Case histories are presented, to illustrate some gross and histologic changes observed and the relatively low incidence of masculinizing changes. In a patient whose remission has persisted for more than eight years, mammary biopsy was performed both before and after a radical mastectomy three years after onset of therapy. There was gross reduction in the size of the primary breast tumor and lymph nodes, but the histologic picture showed no changes. On the other hand, in another patient, impressive histologic changes took place after androgenic therapy. Sex chromatin was observed in some of the tumor cells both before and after treatment; and again at autopsy following hypophysectomy, sex chromatin was found in the skin, adrenal cortex and tumor tissue.

Acknowledgment

The authors wish to express their gratitude to Dr. Edward Henderson of Schering Corporation who provided the generous supplies of testosterone (Oreton F®) used in this study.

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ENVIRONMENT AND AGING

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It is being said that ours is a young nation. This is true historically and still, to some degree, sociologically; however, only to some degree.

Few among us, except sociologists and the statisticians of the U. S. Department of Labor, realize that we are fast becoming a nation of aging people. Since 1935, when Congress passed the Social Security Act, we have come to associate the aged (not the aging) with those over 65 years of age—the minimum age limit which by law entitles an individual to eligibility for financial benefits. At that time, namely 1935, the age of 65 was set arbitrarily, although the lawmakers were aware that aging differs from individual to individual. This is evident physically, emotionally, and socially.

Among the disciplines which deal in services to individuals it is particularly the practitioner of the social sciences who has been trained to see the human being he is serving as an entity, *i.e.*, to consider a medical disorder in the light of emotional and social factors surrounding the disorder, or to consider an emotional illness in the light of accompanying physiologic and social changes. However, for the purpose of this paper, the discussion will be confined strictly to what can properly be called the "social" or environmental aspects of aging.

Formerly people used the phrase "growing old gracefully" when they spoke of senescence. Today they speak of senescence as a "problem" (as everything today seems to be). And a problem it is, as a few statistics may show. During the height of the Roman Empire the average life span was 23 years. It was still only 47 years in this country in 1900, but already 63 years by 1940, and it has been estimated that by 1960 the average life expectancy may reach 75 years. Accordingly, the number of people over 65 has multiplied tremendously. Whereas in 1940 there were approximately 9 million people over 65, there were more than 12 million in 1950. The estimates range from 25 to 36 million people over 65 years of age by 1980. While the over-all United States population increased 7.2 per cent during the decade 1930 to 1940, the age group of 65 or over had an increase of five times that figure. The reasons for our young nation growing rapidly "older" are generally known—better medical services, higher standards of living, improved public health service, a declining birth rate, and even such an apparently insignificant factor as the curbing of immigration. To cite a figure in the State of California: In one of the many district offices of the Bureau of Public Assistance of the County of Los Angeles which administers the Old Age Security Program of the State—the District of Burbank, serving a population of a little over 100,000—there were 8,106 active Old Age grants in November 1956, as compared with less than 3,000 a decade earlier. In the same period (November, 1956) the total number of grants in the State of California was 265,527, as compared with 110,000 less than half a decade earlier.

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What are the social aspects facing our aging population, as distinguished from previous generations? They may be summarized as follows: economic security, employment, housing, medical, psychiatric, and social services, facilities for the care of the chronically ill, sheltered care, adult education, and recreation.

ECONOMIC SECURITY

The concept of economic security in this country dates from 1935, when Congress passed the Social Security Act. The Act was passed as an outgrowth of the depression years. At that time the intention of the lawmakers was not only to grant our senior citizens a minimum subsistence income but, in view of the depression, to eliminate their competing with the younger elements on the labor market. Today, the Social Security Program, although recently amended, augmented and broadened, seems to have less significance to the person over 65 in view of changed circumstances, such as more and better opportunities for work either with or without social security benefits. The picture of grandfather sitting in his easy chair with a pipe has almost vanished from the American scene. Perhaps, what constituted a dire necessity for obtaining economic benefits in 1935 at the age of 65 (because of fewer opportunities for work and a lesser expectancy of life), now the age of 75 seems to be closer to "old age."

Still, economic security is important to our aging population. It seems to me that the core of the problem lies in the individual's ability to work and not in his age. This means preventing a drain on the economy by keeping those people employed who eventually may become recipients of Old Age Assistance and allowing them additional years of financial security through self-maintenance. In this way, the old person can be useful to others and, in addition, keep his self-respect. However, when retiring finally becomes necessary, it should be *to* rather than *from* something. This seems to have been the crucial point in geriatric philosophy during the last twenty years. As one writer pointed out, "Social Security of the pension kind is not at all the answer; with no outlet for muscle or brain, Social Security is unbiologic."

EMPLOYMENT

As is pointed out by the U. S. Department of Labor in its reports on Employment Opportunities for the Older Worker, employers need not, and should not, deny employment to older workers because of the alleged increase in pension and insurance payments. The Department feels it more likely that the costs of the eventual pensions for younger workers will exceed the amount that is currently being put aside for this purpose. The reason given is that the size of the pension usually depends on length of service and final earnings of the individual, and particularly of the younger worker, rather than the older one. A pilot study on the comparative performance of older workers in selected plants in the footwear and men's garment industries shows that there is no significant decline in output per man hour through age 54, and that, on the average, the decline after 55 is smaller than variations within age groups. There is also the aspect of collective bargaining covering older workers. A study of 1,687 collective bargaining agree-

ments covering 7.5 million American workers showed that the worker growing old in the service of the employer is generally assured a greater degree of protection on the job and more liberal benefits than are his juniors in point of service. However, there is persistent evidence of age-prejudice in hiring and discharging in larger firms and in firms with pension plants. Yet the older unemployed compared favorably with the younger unemployed in levels of skill, job stability, and earnings.

HOUSING

According to the Governor of California's Conference on the Problems of the Aging in 1951, it appears that most of California's aged are housed in one of three ways: in a house or apartment in no way designed or built for their needs, but which they happen to own or occupy; with a family of a married child, or occasionally someone else, usually in quarters poorly suited for such arrangements; or in a rooming or boarding house or a third-rate hotel, often in a deteriorating neighborhood. It was the Conference's opinion that "little has been done by either public or private developers to meet these needs whether in California or elsewhere in the nation." The Conference recommended that the Housing Act of 1949 should be amended to include aged couples as well as single people and non-citizens, because these central blighted areas including a large proportion of old people become even more significant when they threaten to hamper the rehousing of people displaced by urban redevelopment operations. The Conference further suggested that social scientists, architects, city planners, business and public interest organizations, public agencies and consumer groups should determine more exactly the extent and nature of the needs, the kind of housing required, the economic means needed to produce such homes, and the most effective program to solve such a problem.

MEDICAL AND PSYCHIATRIC SERVICES

These services are mentioned here as part and parcel of social aspects of the aging. It is this writer's opinion that participation of the aging in medical and psychiatric services should be on the same basis as other age groups. As many citizens know, the aging are not necessarily less healthy than their juniors merely because of their greater age, for physical and mental deterioration varies greatly from individual to individual. For instance, the number of cases of cardiac illness among men under 40 years of age has risen to an alarming degree. Likewise, it appears that, proportionately speaking, the increase of mental illness among the juniors under 45 is alarmingly higher than in those over 45 years of age.

FACILITIES FOR CARE OF THE CHRONICALLY ILL

Because of the tremendous cost of long-term medical care, the increased number of older citizens, and the greater hazards of industrial and traffic accidents, the cost of the care of chronically ill persons who cannot be rehabilitated is becoming excessively high. For instance, it is reported that the Department of

Public Assistance in Pennsylvania has received a grant of $3,000,000 in its budget to provide nursing-home services for its clients, whereas formerly the Department did not pay any special rates for such care. Although this grant may have been prompted by political pressure, the need for such a grant is obvious, since any smaller amount would be insufficient for long-range planning. Facilities as well as funds for the chronically ill will be a sensitive major problem for many years to come.

SHELTERED CARE

Homes for the aged may be the right solution for some senior citizens and not for others. As Rosen and Kostick point out, "many of our older population would be spared the difficult experience of tearing out roots from their own home, family and community," if old age homes had an integrated program in operation—a program which particularly represents economy "in terms of human value." These authors speak primarily of the senior citizen's separation and adjustment problems and raise the fundamental question, "Is the trip to the home really necessary?" They feel that the home for the aged will continue to be a "catch all" as long as nothing is done on a local level to meet the needs of the older population. These authors feel, and in my opinion, rightly, that there are many old people who are able to continue to live in their own homes or with their families, given the combined services of a homemaker, doctor, visiting nurse and social worker under one organized administration, as a recent study of the Welfare and Health Council of New York City has shown. The Home for the Aged then should direct its fullest attention to the *very dependent* aged who need a total protective environment, intensive nursing care and specialized social, mental and medical services.

ADULT EDUCATION

If we perceive the theory that education is an ongoing and never-ending process, it stands to reason that the aging person will not stop in his quest for knowledge just because he has become eligible for the Old Age pension. His quest for knowledge may be pursued on a formal as well as an informal basis. Now and then the newspaper reader is presented with a picture of a grandmother in cap and gown alongside her simultaneously graduating grandchild. I have always been a proponent of informal or, as it is called, "adult education," which pretty much lets the student choose his own course of study. The older person has a disadvantage in a lesser life expectancy; hence, his often greater speed and intensity of study. In a club poll conducted by the Health and Welfare Council of Philadelphia, involving the area's 130 "Golden Age Clubs and Centers" and asking the question "What would you like to learn for fun?" 56 subjects of interest were named by older members; and in the six adult school systems, 124 subjects in which the older pupils were enrolled included some additional categories. Among these subjects were: creative self-expression through drama, music, arts, photography; poise, through etiquette and public speaking; study of the times and people at home and abroad; logic and philosophy; self understanding; homemaking and home improvement skills; the art of lovemaking;

and problems of retirement. These answers were indicative of the need for special thought and planning on the part of the community. Further polling revealed that the older members prefer daytime classes because they are fearful at night and cannot see as well; moreover, in the daytime the weather is more pleasant, they feel less tired, and they need the occupation because time hangs heaviest. They prefer comfortable attractive rooms, but they want their educational classes held at times other than their social meeting periods. They prefer to study with their peer group and to have a teacher who is middle-aged or older. Therefore, the Committee concluded that senior citizens can learn, that many will choose to do so if given a suitable opportunity, and that such learning can enrich their hours of leisure in later life, and improve their mutual health.

RECREATION

Along with adult education, recreation has become a byword among community leaders as well as the aging. Jerome Kaplan, in his book entitled "A Social Program for Older People," devotes about six out of nine chapters to the various aspects of recreation, such as the roles of the social group worker, the volunteer, organization of and programming for a group, and fun in the out-of-doors through camping. Other books, such as "Recreation Activities for Adults," prepared by the staff of the National Recreation Association, or "The Chicago Plan," lend weight to the ever-increasing need as well as importance of recreation in the life of the aging. Essentially, it can be stated that recreational programs and their operations are not much different from those of other age groups, except the very young. Some of the basic structure as well as the aim and scope of the leader in a group of the aging is "generic", *i.e.*, the fundamental principle of leadership as well as interaction among the group members remains the same. Within the group, organization of a new group, sponsorship, subjects of interest, negotiation of new relationships among the members, the budget, facilities, division of responsibilities and roles to be played by the various members are the principal inherent factors. Because of the apparent easiness in getting groups together, recreation seems to be the least of all headaches centering around the aging. For the aging, as for those at other age levels, recreation is as necessary as food and sleep.

The tendency in former years to ignore the needs or even the presence of the minority groups in our age brackets, namely the children and the aging, no longer prevails. Both have become powerful and vociferous minorities and, if the present population trend continues, the aging are on their way to becoming the majority of our population. Moreover, many of us seem to have forgotten that we were once children ourselves, while scolding Johnny for not obeying us. We seem to be oblivious and blissfully blind to the fact that, given time enough, we shall be "old" ourselves one of these days and thus be in the position of being referred to as the aging, instead of speaking about them as we do today.

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NOCTURIA IN THE ELDERLY MALE*

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Nocturia has been associated with malnutrition in time of war and has been frequently reported in World War II as well as in World War I. In clinical practice this troublesome symptom is often seen among elderly males. Malnutrition, hormonal imbalance and aging connective tissue are all factors which should be taken into account. Ruling out surgical urologic conditions, there are many cases of nocturia in the male which can be successfully treated by combined therapy with vitamin B_1, estrogen and a daytime diuretic.

A review of renal physiology is helpful in outlining the principles on which this form of therapy is based.

RENAL PHYSIOLOGY AND PATHOLOGY

The formation of urine depends upon the blood supply to the kidney, filtration through the glomeruli, and reabsorption of the filtrate in the tubules. The functional unit (nephron) consists of a glomerulus, a tubule and the blood supply. The tubule is divided into the proximal and distal convoluted portions and the connecting loop of Henle; there are over a million nephron units in each kidney. One quarter of the blood pumped through the aorta goes to the kidney, and this results in the entire blood supply being filtered by the kidneys sixteen times a day. The blood pressure in the glomerulus capillary is about two and a half times the capillary pressure elsewhere in the body.

The hydrostatic pressure in the glomerulus allows the formation of a filtrate which may amount to 200 liters in twenty-four hours, or about 130 cc. per minute. The fluid shift through the glomerulus increases the viscosity of blood in the efferent arteriole and the resulting resistance at this site produces back pressure which helps maintain filtration pressure within the glomerulus. Because of reabsorption, the flow of filtrate in the proximal tubule is only 24 cc. per minute. Absorption in the loop of Henle diminishes the flow of filtrate to 15 cc. per minute in the distal tubule. Further absorption in the distal tubule leads to the final urine in the collecting tubules, the flow being only 1 cc. per minute.

The glomerulus is a sphere with blood entering and leaving at the vascular pole and filtrate draining off at the opposite, or urinary pole. The blood enters through the afferent arteriole, passes through the many capillaries and leaves through the efferent arteriole. The filtrate passes through a basement membrane which is markedly convoluted and then into the urinary space of Bowman's capsule. The basement membrane is the intercellular substance between the en-

* Presented at the Annual Meeting of the American Geriatrics Society, New York, N. Y., May 30 and 31, 1957.

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dothelial cells of the capillary wall; these cell bodies seem to gravitate toward the axis of the glomerulus. The intercellular substance pouches out between the cells to produce convolutions, which provide maximum surface for the filtration membrane. The juxtaglomerular cells may be sensitive to changes in filtration and may secrete a hormone to maintain hydrostatic pressure within the glomerulus and thus maintain filtration. This hormone may account for the Goldblatt kidney phenomenon.

The filtration membrane has a thick, dense middle layer of intercellular substance or ground substance, and on the blood-space side is covered with a thin cytoplasmic extension from the capillary endothelial cell.

The dense layer of the basement membrane has many fine pores that allow the passage of larger molecules up to a weight of 70,000. These pores allow hemoglobin to pass through, but hold back serum albumin. In experimental animals, when one kidney is removed, the remaining kidney increases in size due to an increase in the amount of ground substance. This material is constantly being built up and broken down in the body, and the breakdown permits the excretion into the urine of some of the mucopolysaccharides that compose the ground substance. These materials in the urine, especially chondroitin, prevent the aggregation of calcium molecules and keep the calcium salts in suspension even when the urine becomes a supersaturated solution, thus preventing the formation of calculi.

In eclampsia, adverse action on the ground substance by multiple hormones from the placenta may impair filtration. The vaso-excitor material (VEM) from the renal hormone cells raises blood pressure to maintain filtration. A vaso-depressor material (VDM) made in the liver acts to restore homeostasis. The breakdown of the homeostatic mechanism terminates in convulsions and coma.

In the aged kidney the glomerular filtration rate is reduced from a normal of almost 200 liters in twenty-four hours to about 120 liters. The formation of about 1.5 liters in twenty-four hours in a normal kidney becomes an average of about 1.0 liter in the aged kidney.

Antidiuretic hormone (ADH) affects the rate of tubular reabsorption in the normal kidney; it acts on the distal tubule and increases the reabsorption of water. It also inhibits reabsorption of sodium chloride. This hormone is formed in the posterior pituitary when activated by the supraoptic nucleus (in the hypothalamus); the two are connected through a special nerve tract. Fluid losses elsewhere in the body stimulate the formation of ADH in order to recover a larger amount of fluid from the glomerular filtrate. Normal sweating during sleep promotes the formation of ADH at that time. In starvation, hormone production may be insufficiently responsive or even totally nonresponsive to stimuli; for instance, lack of thiamin (an antineuritic vitamin) decreases the ability to produce ADH. It is possible that the hypothalamus or the tract between the supraoptic nucleus and the pituitary may be affected.

A hormone of the adrenal cortex, desoxycorticosterone, is opposite in effect to ADH. It maintains filtration at the glomerulus and inhibits water reabsorption in both the proximal and distal tubules. In addition, it promotes the formation of liver enzymes that inactivate ADH. Urine formation is involved in the many

metabolic interrelationships between the kidney and the other organs. Homeostasis is maintained by the push-pull effect of integrated pairs of hormones.

The distribution of body water in the physiologically aged patient differs from that in the young adult. In the aged, the extracellular water (plasma and interstitial space) constitutes 25 per cent of the total body weight, whereas in the young adult it constitutes 18 per cent. Ground substance, the water-holding gel of the interstitial space, is more scanty in the elderly. The aging of skin and sweat glands results in diminution of insensible perspiration as well as active sweating. In the aged patient there is a need for interstitial space drainage, which must be carried out by kidneys of diminished capacity. The kidneys must function actively even during sleep in order to maintain the water balance. Malnutrition may aggravate the waterlogging, as may chronic heart disease with insidious failure.

Variations in urine formation result from the varying renal blood flow related to muscular activity, emotional states, and changes in the food and fluid intake. For example, the pattern of diuresis caused by drinking tea is different from that caused by drinking large amounts of water. Medications such as diuretics increase the volume of urine by inhibiting tubular reabsorption and may alter the electrolyte pattern of the plasma. Chronic disease or even injury will affect kidney function and urine flow.

DIAGNOSIS AND THERAPY

Before treating a case of nocturia medically, surgical urologic disease must be ruled out. If the nocturia is caused by obstruction from prostatic hypertrophy, treatment must be directed toward the relief of obstruction. The diagnosis is made by means of rectal examination, measurement of the residual urine after voiding, and by the history of acute retention. In organic disease of the bladder wall in association with cystitis there is sufficient irritability to diminish bladder capacity and cause nocturnal micturition. Chemical irritation of the bladder wall from excess oxalates in the urine may also cause nocturia. The oxaluria may be related to a preponderance of certain vegetables in the diet, or there may be an inherited metabolic defect that predisposes to oxaluria with only a small amount of dietary indulgence.

Of special interest is the fact that nocturia occurs in association with prostatic hypertrophy, even in the absence of obstruction. The prostate is a hormone-dependent tissue and an imbalance between androgenic and estrogenic hormone in the elderly leads to prostatism. The concept of hormone-dependent tissue is the basis for the treatment of prostatic cancer by castration and for the treatment of metastatic breast cancer by chemotherapy. Prostatic hypertrophy in the aged can be successfully controlled by the use of estrogenic hormone. In the general supportive treatment of the elderly patient, combined estrogen-androgen therapy is an established practice, and appears to retard the degenerative processes. In gynecology, estrogenic hormone is effective in diminishing irritability of the lower urinary tract, and in controlling urethral caruncle in postmenopausal women.

With surgical urologic disease ruled out, many cases of nocturia in the male

may be effectively treated with vitamin B_1, estrogen and a daytime diuretic. To avoid the effects of malnutrition, thiamin chloride (vitamin B_1) is given in a dosage of 25 mg. three times a day. Estrogenic hormone may be given intramuscularly in oil in weekly injections or by mouth in the form of stilbestrol, 0.5 mg. three times a day. A diuretic is used that will increase the formation of urine during the waking hours. Rolicton has a diuretic action beginning one hour after administration and lasting up to eight hours afterward. Thus, if taken at breakfast and at lunch it helps to control nocturia.

CONCLUSION

Troublesome nocturia in the elderly male may in some instances be due to general aging of connective tissue, which permits increased hydration of the skin, kidney, and interstitial spaces. Malnutrition, and hormonal imbalance may also be factors. In such cases of nocturia in the male, malnutrition is controlled by administration of vitamin B_1, and estrogen therapy retards some of the effects of aging, by restoring a favorable hormone balance. Stimulation of water excretion during the day by a suitable diuretic is also a useful measure in the management of nocturia.

A CLINICAL EVALUATION OF MEPHENTERMINE SULFATE AND PENTYLENETETRAZOL AS STIMULANT THERAPY FOR THE GERIATRIC PATIENT

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Within the recent past, there has been increasingly widespread use of ataractic or "tranquilizing" drugs. These drugs have been used extensively for the suppression of neurotic manifestations in patients of almost all age groups, both in the hospital and on an outpatient basis. The objectives of this therapy have been to enable patients to tolerate real or imagined stresses and to convert hyperactive, unmanageable patients into more docile, cooperative ones. The ataractic drugs have achieved these objectives in a highly effective manner.

Conversely, there has been a continuing search for suitable and effective stimulant drugs for the geriatric patient. The senile patient is particularly prone to exhibit apathy and progressively diminishing ambulation. These are the first steps toward the eventual development of insidious "intercurrent" pneumonia and decubitus ulcers. Such developments are a continuing source of frustration as regards both medical and nursing care. Perhaps at least a partial solution is offered by stimulating the patient into activity. The stimulant drugs may prove to be effective in preventing pneumonias and decubitus ulcers in elderly patients.

The evaluation of stimulant drug therapy for the geriatric patient was approached in the following manner:

First, it was necessary to choose suitable drugs. Available facilities limited the choice to 2, which were chosen for their special qualities. One of these drugs, pentylenetetrazol, has been previously evaluated as a geriatric stimulant and found effective by Smigel, Serhus and Barmak (1). In a study of the effect of pentylenetetrazol (oral) upon 20 patients over a three-month period, these investigators reported significant beneficial change in orientation, fatigue, appetite, activity, and hemoglobin level in the majority. The dosage of pentylenetetrazol[1] used was 0.200 Gm. by mouth four times daily for three months. The pharmacologic properties of this drug are well known. Its main action is to stimulate the central nervous system. Pentylenetetrazol is described as a relatively nontoxic drug, in so far as the amount necessary to produce serious poisoning is concerned (2).

The second drug chosen for evaluation was mephentermine sulfate[2] (N-methylphenyl-tertiary-butylamine sulfate). It has been described as a pressor agent, exerting action mainly by peripheral vasoconstriction; it is also a central

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[1] Metrazol, supplied through the courtesy of Bilhuber-Knoll Corp., Orange, New Jersey.

[2] Wyamine, supplied through the courtesy of Wyeth Laboratories, Philadelphia, Pennsylvania.

nervous system stimulant, though this action is much less than that of other sympathomimetic amines with an unsubstituted aromatic nucleus (3). A study (4) with oral mephentermine sulfate has been conducted at the Jefferson Medical College in Philadelphia, Pennsylvania, upon a group of 44 patients suffering from a variety of chronic illnesses, primarily to determine the effect of the drug, 1) upon mood, and 2) in increasing blood pressure in the ambulatory hypotensive individual. A definite improvement in mood was noted in nearly all of the patients, and in those with hypotension there was an adequate blood pressure response. Patients in the hypotensive group received mephentermine sulfate in a dosage of 0.025 Gm. one to three times daily. Side-effects such as insomnia, nervousness, and excitability were evident in 2 of the 44 patients. It was the opinion of the investigators that there was no evidence of habituation or untoward reactions coincident with long-term therapy. Mephentermine has approximately one-third to one-half the potency of amphetamine or desoxyephedrine as a cerebral stimulant for chicks, cats or dogs (5). By means of determining the LD_{50} in mice, it was found that mephentermine was two-thirds as toxic as amphetamine or desoxyephedrine and three times more toxic than ephedrine (6).

METHODS

Sixty-five essentially unselected elderly patients (32 women on one ward and 33 men on another) were treated in such a way that during the first month one group received mephentermine sulfate in a dosage of 0.025 Gm. orally three times daily, while the other group received pentylenetetrazol in a dosage of 0.200 Gm. orally three times daily. The drugs were administered at 6:00 A.M., 10:00 A.M. and 2:00 P.M. Then for one week no stimulant drug was given. At the beginning of the fifth week, the drugs were started again; but the medication was reversed for the two groups and continued for four weeks. The aforementioned dosages were used throughout the investigation. Thus, at the end of the nine-week study, each patient had undergone a four-week trial of mephentermine sulfate therapy and a four-week trial of pentylenetetrazol therapy. Three patients (female) were excluded from the study because of a diastolic blood pressure above 90 mm. Hg, due to the vasopressor action of mephentermine sulfate.

A practical method of evaluating the effect of therapy was sought. It was decided to use a primarily objective approach in evaluating any change brought about by medication in such basic qualities as orientation, activity status, continence, mood (subjective and/or objective appraisal), appetite, and self-feeding ability. Laboratory studies were not deemed necessary because of the extensive pharmacologic data on these relatively nontoxic drugs. It was also felt that such studies as hemoglobin determinations would be only a secondary reflection of the general nutritional state of the patient. The patients were evaluated before beginning the study, at the end of the fourth week, and at the end of the ninth week. The observations of the ward nurses and aides were utilized liberally in attempting to arrive at accurate appraisals, as the ward aides would be the first to notice any significant change in such a quality as the degree of continence.

The great majority of the patients in this study were suffering from long-

established chronic diseases—mostly based on arteriosclerotic changes. The average age for the entire group was 73 years (with a range of 53 to 95 years). In the women, therapy was started with pentylenetetrazol, and in the men with mephentermine sulfate. Of the group of 65 patients, 48 received pentylenetetrazol; 17 men were not given the medication (2 refused, and 15 were not good candidates for continued stimulant therapy, mainly because of hyperactivity or uncooperativeness). A total of 55 patients received mephentermine sulfate; 10 were not given the medication (2 refused, and 8 women were not good candidates because of hyperactivity or uncooperativeness).

RESULTS

The data on the effects of these drugs in the 65 patients are listed in Table 1.

Of the 48 patients who received pentylenetetrazol, 15 or 31 per cent exhibited definite improvement of some degree, 17 or 35 per cent had unpleasant side-effects, and 16 or 33 per cent were unchanged.

Of the 55 patients who received mephentermine, 23 or 42 per cent exhibited definite improvement, 21 or 38 per cent had unpleasant side-effects, and 11 or 20 per cent remained unchanged.

DISCUSSION

These results are presented in terms of percentages merely for the sake of convenience. The data are too few to be statistically significant; however, they do seem to have some qualitative significance. By this is meant that *any* improvement in the status of these chronic geriatric patients is respectfully viewed as an achievement.

The unpleasant side-effects consisted mainly of either hyperactivity and uncooperativeness, or nausea (rarely with emesis). These reactions occurred with approximately equal frequency. The two drugs appeared to produce the same types of side-effects; this was not surprising in view of their basic actions.

It is of interest that 3 patients tolerated pentylenetetrazol, but not mephentermine sulfate; and 4 patients tolerated mephentermine sulfate, but not pentylenetetrazol. The explanation for this is not apparent at present.

Almost all the unpleasant side-effects appeared to be the direct result of too much stimulation of the central nervous system, and probably could have been eliminated by decreasing dosage according to the needs of the individual patient. Similarly, it is believed that a number of the patients in whom there was no apparent change during medication could have been benefited by increased dosage according to individual need. The necessity for economy of time prevented the author from carrying out these fine adjustments in individual dosage.

It appeared that neither of these drugs caused any significant tranquilizing change in the mood of these patients, as evaluated subjectively and/or objectively—contrary to the findings of Smigel (7). This study revealed that the basic personality structure and reaction patterns of the patients were merely reinforced by these stimulant drugs. Thus, a patient who was slightly uncooperative, confused and agitated prior to being given stimulant medication would

TABLE 1

Data on 65 Patients Receiving Pentylenetetrazol or Mephentermine

Patient				Diagnosis	Orientation			Level of Activity	Continent	Subj. and/or Obj. Mood	Appetite*	Effect of Pentylenetetrazol	Effect of Mephentermine
No.	Name	Sex	Age		Time	Place	Person						
1	L.B.	F	74	ASHD**	Yes	Yes	Yes	Ambulatory	Yes	Depressed	Fair	0	Calm; occas. euphoric
2	B.B.	F	56	HCVD** & CVA**	Yes	Yes	Yes	Wheelchair	No	Calm; occ. euphoric	Good	Walks occas., assisted	0
3	E.C.	F	76	HASHD**	No	Yes	Yes	Walker	Yes	Calm	Good	Ambulatory	0
4	F.C.	F	84	Fracture left femur	No	No	Yes	Wheelchair	No	Calm	Fair	0	0
5	B.D.	F	74	ASHD	No	Yes	Yes	Wheelchair	No	Euphoric	Fair	Uses walker; occas. cont.; appetite good	Ambulatory; cont.
6	S.C.	F	75	Osteoporosis	Language barrier			Bedridden	No	Calm	Good	Talks occas.	Talks occas.
7	L.M.	F	65	CVA	No	Yes	Yes	Ambulatory	No	Calm	Fair	Occas. agitated	Occas. agitated; poor appetite
8	S.S.	F	72	Carcinoma of breast	No	Yes	Yes	Wheelchair	No	Calm; occ. depressed	Fair	Oriented in time; appetite good	Calm; never depressed; oriented in time
9	H.B.	F	78	CVA	Aphasic			Bedridden	No	Calm	Good	Occas. irritable; appetite fair	Occas. irritable
10	P.A.	F	78	ASHD	Yes	Yes	Yes	Walker	Yes	Depressed	Fair	Hyperactive & uncooperative	Ambulatory
11	S.G.	F	79	CVA	Aphasic			Bedridden	No	Euphoric	Fair	Seizure	Seizure
12	H.S.	F	85	HCVD	No	Yes	Yes	Bedridden	No	Calm	Fair	Nausea	Nausea
13	B.L.	F	71	ASHD	Yes	Yes	Yes	Wheelchair	Yes	Calm	Good	0	Nausea; dizziness
14	F.V.	F	90	Fracture rt. femur	No	No	No	Wheelchair	No	Calm; occas. belligerent	Fair	Poor appetite	Refused
15	M.H.	F	77	ASHD	Yes	Yes	Yes	Bedridden	Yes	Calm	Fair	Nausea	Nausea
16	E.T.	F	82	Essential hypertension	Yes	Yes	Yes	Ambulatory	Yes	Calm	Fair	Hyperactive & uncooperative	Hyperactive & uncooperative
17	M.T.	F	80	HCVD	Yes	Yes	Yes	Ambulatory	Yes	Calm	Good	Hyperactive & uncooperative	Hyperactive & uncooperative
18	J.N.	F	89	Fracture left femur	Language barrier			Bedridden	No	Depressed	Good;	Opens eyes	Opens eyes

17	M.T.	F	80	HCVD	Yes	Yes	Yes	Ambulatory	Yes	Calm	Good	Hyperactive & uncooperative	Hyperactive & uncooperative
18	J.N.	F	89	Fracture left femur	Language barrier			Bedridden	No	Depressed	Good; hand-fed	Opens eyes	Opens eyes
19	J.S.	F	83	Osteoarthritis	Yes	Yes	Yes	Bedridden	Yes	Calm	Fair	0	0
20	E.H.	F	68	ASHD	Yes	Yes	Yes	Ambulatory	Yes	Calm	Good	Postural hypotension	Appetite very good
21	S.W. (expired)	F	76	Fracture rt. femur	No	Yes	Yes	Wheelchair	Yes	Depressed	Fair	Nausea & vomiting	Nausea & vomiting
22	J.T. (expired)	F	64	Diabetes mell.	Yes	Yes	Yes	Wheelchair	Yes	Calm; occas. agitated	Good	Nausea	Walks with assist.; agitated more often
23	A.M. (expired)	F	95	CVA	No	No	No	Bedridden	No	Depressed	Poor; tube-fed	More verbal response	More verbal response
24	L.W. (expired)	F	60	ASHD	No	No	Yes	Wheelchair	No	Euphoric	Good	Occasional cont.	0
25	M.N. (discharged)	F	79	Osteoarthritis	Yes	Yes	Yes	Wheelchair	Yes	Calm	Fair	Ambulatory	—†
26	M.V. (discharged)	F	79	ASHD	Yes	Yes	Yes	Ambulatory	Yes	Calm	Good	Nausea	—
27	E.W. (expired)	F	83	ASHD	No	No	No	Bedridden	No	Calm	Very poor; hand-fed	0	—
28	E.K.	F	66	HCVD	Yes	Yes	Yes	Wheelchair	Yes	Calm	Good	Nausea	—
29	V.P. (transferred)	F	87	Diabetes mell.	No	No	No	Bedridden	Yes	Calm; often belligerent	Good	Oriented in place	—
30	E.S. (transferred)	F	80	CAS**	No	No	No	Ambulatory	Yes	Calm	Good	Hyperactive & uncooperative	—
31	R.W. (transferred)	F	88	CVA	No	No	Yes	Bedridden	No	Calm; occas. belligerent	Fair	0	—
32	I.V. (transferred)	F	77	HCVD	No	No	No	Bedridden	No	Calm; occas. fearful	Fair	0	—
33	C.J.	M	63	CVA	No	No	Yes	Wheelchair	No	Calm; occas. agitated	Good	Oriented in time	Oriented in time
34	P.N.	M	74	HCVD	No	No	Yes	Bedridden	No	Calm; occas. agitated	Good	—	0

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TABLE 1—*Continued*

Patient				Diagnosis	Orientation			Level of Activity	Continent	Subj and/or Obj. Mood	Appetite*	Effect of Pentylenetetrazol	Effect of Mephentermine
No.	Name	Sex	Age		Time	Place	Person						
35	A.C.	M	76	ASHD	No	No	Yes	Wheelchair	No	Belligerent	Good	Nausea	0
36	C.P.	M	67	CVA	Yes	Yes	Yes	Wheelchair	No	Apathetic	Good	More alert	More active in wheelchair
37	A.B.	M	57	CVA	Deaf Mute			Ambulatory	Yes	Calm; occas. euphoric	Good	Refused	Hyperactive & uncooperative
38	T.S.	M	56	CVA	No	No	Yes	Bedridden	No	Belligerent	Good	Very belligerent	Hyperactive & uncooperative
39	P.A.	M	60	CVA	Aphasic			Wheelchair	Yes	Depressed; occas. belligerent	Good	Refused	Refused
40	C.C.	M	80	ASHD	No	No	Yes	Wheelchair	No	Calm	Good	Uses walker	Hyperactive & uncooperative
41	J.D.	M	84	ASHD	No	No	Yes	Bedridden	No	Calm	Poor; occas. hand-fed	—	Hyperactive
42	J.A.	M	86	ASHD	Aphasic			Wheelchair	No	Calm	Good	0	More cooperative
43	M.P.	M	58	CVA	Aphasic			Wheelchair	Yes	Calm	Good	0	0
44	T.H. (transferred)	M	79	ASHD	No	Yes	Yes	Wheelchair	Usually	Belligerent	Good	—	Oriented in time; walks assisted; more cont.
45	H.H.	M	85	HCVD; CVA	No	No	Yes	Bedridden	No	Belligerent occas.	Good	0	Wheelchair; occas. less belligerent
46	W.T.	M	67	Cor pulmonale	Yes	Yes	Yes	Ambulatory	Yes	Belligerent occas.	Good	0	0
47	M.S.	M	76	ASHD	No	Yes	Yes	Bedridden	Yes	Belligerent occas.	Good	0	Wheelchair
48	O.H.	M	73	Senile emphysema	No	Yes	Yes	Bedridden	No	Calm	Fair	0	Good appetite
49	W.N.	M	66	HCVD & CVA	No	No	Yes	Bedridden	No	Belligerent	Good	0	Hyperactive & uncooperative
50	L.R.	M	54	CVA	Yes	Yes	Yes	Wheelchair	No	Euphoric	Good	0	More alert; very good appetite
51	S.K.	M	53	Bilat. stasis ulcers	Yes	Yes	Yes	Wheelchair	Yes	Euphoric	Good	Very alert; walker	On crutches occas.; more alert

50	L.R.	M	54	CVA	Yes	Yes	Yes	Wheelchair	No	Euphoric	Good	0	More alert; very good appetite
51	S.K.	M	53	Bilat. stasis ulcers	Yes	Yes	Yes	Wheelchair	Yes	Euphoric	Good	Very alert; walker	On crutches occas.; more alert
52	A.P.	M	60	Abd. aortic aneurysm	Yes	Yes	Yes	Wheelchair	No	Calm	Good	Occas. cont.	Walks occas., with assistance
53	A.B. (expired)	M	73	Spinal cord tumor	Yes	No	Yes	Bedridden	No	Euphoric	Good	0	Wheelchair; strapped in
54	A.S. (expired)	M	56	Arterioscler. obliterans	Yes	Yes	Yes	Wheelchair	Yes	Occas. depr.	Poor	—	Nausea
55	R.T. (transferred)	M	68	CVA	Yes	No	Yes	Wheelchair	No	Depressed	Fair	—	Hyperactive and uncooperative
56	J.L. (transferred)	M	54	Laennec's cirrhosis	Yes	Yes	Yes	Ambulatory	Yes	Calm	Good	—	More active
57	H.H. (transferred)	M	82	ASHD	Yes	Yes	Yes	Ambulatory	Yes	Euphoric	Good	—	Urinary retention
58	F.D. (transferred)	M	72	Peptic ulcer	No	No	Yes	Bedridden	Yes	Euphoric	Good	—	More alert
59	W.D. (transferred)	M	69	Ulcer & CVA	Aphasic			Wheelchair	No	Calm	Good	—	Comprehends better
60	N.T. (transferred)	M	71	Cor pulmonale	Yes	Yes	Yes	Bedridden	Yes	Apathetic	Poor	—	0
61	Q.H. (expired)	M	74	Chron.pyelonephritis	No	No	Yes	Wheelchair	No	Calm	Fair	—	Nausea
62	W.S. (discharged)	M	89	ASHD	No	Yes	Yes	Ambulatory	Yes	Euphoric	Good	—	Oriented in time; walks with aid
63	G.M. (transferred)	M	66	CVA	No	No	Yes	Wheelchair	Yes	Calm	Good	—	Poor appetite
64	K.K. (discharged)	M	74	ASHD	No	Yes	Yes	Wheelchair	No	Calm	Good	—	0
65	F.C. (expired)	M	78	HCVD	No	No	Yes	Ambulatory	No	Depressed	Good	—	Uncooperative

* With the few exceptions noted in the table, all patients could feed themselves.

** ASHD = Arteriosclerotic heart disease.
HCVD = Hypertensive cardiovascular disease.
CVA= Cerebrovascular accident.
HASHD = Hypertensive arteriosclerotic heart disease.
CAS = Cerebral arteriosclerosis.

† Drug not given.

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almost invariably become completely unmanageable after receiving mephentermine sulfate or pentylenetetrazol. Moreover, there appeared to be no significant increase in the basic intelligence of the patients following either of the two drugs. The occasional improvement in orientation with either drug might well be explained as a direct result of stimulation.

During the course of the study, 9 patients died, 12 were transferred and lost to the study, and 4 were discharged from the hospital.

Perhaps the best criterion of the effectiveness of these stimulant drugs was the enthusiastic response of the ward aides and nurses, whose lessened work-load served as excellent motivation for requesting that the stimulant drugs be continued beyond the nine-week period of the study.

SUMMARY AND CONCLUSIONS

A group of 65 unselected, chronically ill geriatric patients were treated for four weeks with oral pentylenetetrazol and then for four weeks with oral mephentermine sulfate in an attempt to evaluate the effects of stimulant therapy upon their basic condition. The patients suffered predominantly from the effects of arteriosclerosis—particularly the cerebral and cardiac effects—and many had had cerebrovascular accidents.

Significant improvement occurred in approximately one-third of the group. The improvement was noted mainly in their activity status, orientation and appetite (in descending order) and was believed to be primarily due to stimulation of the central nervous system.

No serious side-effects of either medication were observed. Mild side-effects were abolished by altering the dosage.

The effectiveness of mephentermine sulfate was roughly comparable to that of pentylenetetrazol. Mephentermine sulfate acts as both a mild CNS stimulant and a vasopressor, whereas pentylenetetrazol exerts its main effect by CNS stimulation alone.

Thus, hypertension is a contraindication to the use of mephentermine sulfate, and prior irritability and basic uncooperativeness seem to contraindicate the use of either stimulant drug.

Long-term therapy with stimulant drugs appears to be a valuable adjunct in the medical management and nursing care of selected, chronically ill, geriatric patients.

Acknowledgments

The author gratefully acknowledges the assistance of (Mrs.) Louise Harrell, Supervising Nurse (R.N.), Fairmont Hospital, and her staff—in particular, (Mrs.) Selma E. Seidell, Head Nurse (R.N.); the cooperation of Miss Mabel Lew, Pharmacist, Fairmont Hospital; and the valuable constructive criticism of Dr. Robert J. Parsons, Director of Laboratories, Alameda County Hospitals.

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HOST-TUMOR ANTAGONISM. X. RADIATION—A DOUBLE-EDGED SWORD*

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INTRODUCTION

X-ray radiation has been, and will undoubtedly continue to be, one of the greatest single contributions to the practice of medicine. Nevertheless, because of the other sources of radiation that have now been added to our daily life and which we cannot control at present, the medical uses of roentgen rays should be cut to the barest minimum consistent with the best interests of the patient. These best interests may not always be served by the large amounts of radiation that are now given to the patient in both therapeutic and diagnostic radiology. This essay discusses the hazards involved in the legitimate medical uses of radiation, as well as the dangers involved in merely living in this atomic world.

I. RECAPITULATION

In another essay of this series (1), the point was made that in our anxiety to destroy tumor cells by using the maximum safe dose of radiation, we may destroy the patient's immune responses, so that ultimately the tumor may recur. It might be worth while to cite the proofs for this statement.

Murphy (2) showed experimentally that the lymphoid elements are of the greatest importance in immunity to cancer implants. In a susceptible host, that supported a growing tumor, the lymphoid tissue underwent marked degenerative changes. He showed that experimentally-produced variation in the amount and activity of lymphoid tissue is directly correlated with a variation in the resistance of the animal to cancer. Murphy and his colleagues showed that the lymphoid tissue could be practically depleted by repeated doses of x-rays, and could be stimulated by single small doses of x-rays.

When Murphy (2) used doses of x-rays sufficient to deplete the lymphoid tissues, the resistance of mice to tumor transplants was lowered. He questioned whether intensive x-ray therapy in man may not interfere with the defensive mechanism—immunity to tumor formation. It is well known, however, that x-ray therapy of skin cancer is remarkably effective, and there must be a good reason for this. Murphy pointed out that in the treatment of skin cancer, the dosage of x-ray is applied over too small an area to cause any effect on resistance. He believed that x-ray therapy confers a localized immunity to the cutaneous area and makes it unsuitable soil for tumor growth. However, this refractory state is strictly confined to the skin layers, and does not even extend to the underlying connective tissue.

* Parts I–IX of this study have been published in the July, August, November (1956), April, May, June, August, October and November (1957) issues of the Journal.

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Murphy also believed that the therapeutic value of x-ray radiation in cancer depends on the reaction of normal tissues around the neoplasm. Spontaneous skin cancers in mice disappeared promptly after a mild erythema dose of x-rays, but when the tumor was removed later and implanted again in an untreated area, it would grow again. Conversely, when a graft was implanted in an area previously treated with x-rays, degenerative changes occurred in the cancer cells, even though the cells themselves had not been treated. Differences of opinion have been expressed on this point by various authorities (3–5).

The effect of total body irradiation on the immune mechanism in experimental animals, as judged by the antibody response to injected antigens has been documented many times. Hektoen (6) demonstrated in 1915 that total body irradiation suppresses the antibody response to injected antigens in experimental animals. Jacobson and associates (7) extended these observations, and found that when the spleen or the appendix was shielded during irradiation and the antigens subsequently injected, the antibody response (although depressed) rose higher than in non-shielded animals. An explanation for the differences was found in the complete disintegration of lymph nodes within the first twenty-four hours after total body irradiation. In the shielded rabbits, lymphocyte regeneration occurred by the fourth day, whereas in unshielded animals it is usually started by the twelfth day. In spleen or appendix-shielded animals, antibody production could be initiated in these organs, so that by the fourth or fifth day regenerated lymphatic tissue in other parts of the body could take over.

II. THE NATURE OF IONIZING RADIATION

In recent years, radiotherapy has made phenomenal strides by introducing powerful x-ray machines in the million-volt range. However, the potential of these machines in radiotherapy is extremely limited, primarily because of the slight difference in sensitivity between normal and tumor tissue. Further improvement in the effects of radiotherapy will undoubtedly come from attempts to widen the sensitivity difference between these tissues. The best review known to the author of the biologic effects of radiation is that by Lorenz and Congdon (8), and liberal quotations will be made from this source.

The action of ionizing radiation, of which x-ray radiation is one example, is both "direct" and "indirect." The direct action causes ionization of living matter and leads to the disassociation of this matter into free radicals and atoms, with consequent destruction of enzymes and the denaturation of protein. Since living matter consists at least partly of water, the ionization gives rise to H^+ and OH^- radicals, which themselves also react with proteins and enzymes; this is called the indirect action.

When an animal is given a dose of radiation that is 100 per cent lethal, death is caused by pancytopenia with overwhelming infection and intractable hemorrhage (8). This hemorrhagic syndrome is characterized by an extremely low red blood cell count (about 1,000,000), a platelet count usually less than 10,000, severe leukopenia, and bleeding into various organs and tissues. The syndrome is probably the result of damage to the vascular bed by the radiation. Large

numbers of erythrocytes are diverted into the lymphatic system (9). This diversion can be prevented by massive transfusions of platelets—a fact which seems to indicate that the platelets are essential in the maintenance of the integrity of the vascular bed. Other factors are also involved, since even if injection of platelets can modify the syndrome, all the animals subsequently die of overwhelming bacterial infection (10).

There has been much research regarding methods for the modification of radiation injury. These are necessarily of two types: one, to neutralize a part of the radiation, and the other to stimulate the hematopoietic tissues into rapid recovery. The first type involves such procedures as the injection of reducing substances (*e.g.*, cysteine and reduced glutathione) before radiation, and the injection of anoxia-producing substances (nitrites or cyanides) or the production of an anoxic state with low oxygen tension during irradiation (11). Cysteine and reduced glutathione may conceivably work through becoming oxidized by the radicals formed during radiation of the water content of the body—thus removing these radicals. Protection of the spleen during irradiation is also important in the prevention of damage.

The second type of modifying treatment is applied after radiation, because material administered beforehand is itself subject to radiation damage. The principal methods are the injection of a suspension of splenic tissue, or the injection of bone marrow following irradiation. Modification of radiation injury by the substances which are applied afterward is probably effected through stimulation and regeneration of the hematopoietic system (12). Another factor that merits consideration is that the undamaged tissue of bone marrow or spleen that is injected serves as a focus of hematopoiesis to tide the animal over until its own marrow can function again (13).

Total body irradiation can produce lymphoid tumors in mice (14). A systematic study of the factors involved in their production could add to our knowledge of the biology of radiation. Lymphoid tumors induced by total body irradiation originate in the thymus and later spread to other organs and tissues. Thymectomy prevents the induction of the disease, as does shielding of half of the body. Lead-shielding of one thigh, protection of the spleen, and injection of bone marrow (post-radiation) also modify the production of lymphatic tumors. These procedures probably result in the rapid recovery of hematopoietic tissues involved in total body irradiation. On the other hand, prolonged hypoplasia of the bone marrow or lymphoid structures may precede the induction of lymphoid tumors (15).

Some authors have found that estrogens cause a synergistic effect on irradiation in the production of lymphoid tumors (16). This may be because estrogens induce leukopenia within ten to fourteen days after injection (17). Alternatively, testosterone reduces the tendency to development of lymphoid tumors, if administered at the same time as the irradiation (18), an effect which is also obtained by the use of cortisone administered similarly, or even if started as late as six weeks after irradiation (19). The mechanism of this inhibition is not known, but apparently it is not stimulation of the irradiated bone marrow, because

there is actually a decrease in the survival rate of mice treated with cortisone daily after total body irradiation.

Although the induction of lymphoid tumors by total body irradiation appears to be a peculiarity in mice and rats, it is of interest that in humans exposed to the radiation of the atom bomb there was a significant increase in the incidence of leukemia.

It is known that a synergistic effect results when the tumor and the body are irradiated at the same time (8). Starvation also acts as a synergistic factor, conceivably due to the low blood sugar level in starved animals (20). Regression of the tumor occurs more frequently following intravenous hydrogen peroxide when the injection is given simultaneously with the irradiation, or nearly so (21). The exposing of tumor-bearing mice to 95 per cent oxygen and 5 per cent carbon dioxide prior to, and during irradiation also causes a marked increase in the frequency of tumor regression (21).

Radioresistance may be caused in part by a state of anoxia of the tumor. This situation may be found in rapidly growing tumors in which the blood supply cannot keep pace with the growth, or following repeated radiation of a tumor with consequent damage to its blood supply (8).

Lorenz and Congdon (8) believe that from a purely physical point of view it would be hopeless to attempt complete destruction of a tumor by irradiation, even if great differences in radiosensitivity were shown to exist between the tumor and the surrounding tissue (8). This is due to the fact that the absorption process of radiation is not uniform, and therefore radiation cannot kill every tumor cell even if very large doses are given.

Since it is well known that certain tumors may regress permanently after radiation, the state of the tumor bed must be very important in therapy. Lorenz and Congdon believe that effect of radiation on the vascular supply of the tumor is a salient feature. They suggest that there may also be a systemic effect in radiation treatment, for in certain cases of lymphoid tumors, treatment directed to a local area may be associated with regression in distant sites.

Murphy (2) showed that serum collected from an animal after an exposure to x-rays or dry heat had a definite stimulating effect on lymphoid cells *in vitro*. He felt that the radiation treatment caused chemical changes in the body fluids capable of stimulating the lymphocytes.

Vermund and Stenstrom (22) believe there is a differential sensitivity to radiation between malignant and normal tissues; in fact they consider the differential to be the most essential prerequisite for successful radiation therapy.

Successful radiotherapy of malignant tumors results in softening and regression of the mass, healing of ulceration and proliferation of granulation tissue with scar formation. Microscopic examination shows that under the most optimal conditions cancer cells disintegrate, are absorbed by macrophages, and are replaced by fibroblasts growing in from the surrounding tumor bed. The relative influence that this radiation-induced change in the tumor bed has on the regression of the tumor is still disputed.

Following radiation therapy, certain characteristic changes occur in tumors

after a latent period of several days. Early, even though the tumor cells appear intact, there are dilatations of the small blood vessels, both capillaries and lymphatics. There are accumulations of leukocytes and mononuclear cells around the strands of tumor cells. The earliest effect of radiation on the tumor cells is inhibition of mitotic activity. Chromosomes may stick together to form bridges, the chromatin threads may break, and cytoplasmic changes may also occur. Biochemically speaking, it is known that the important SH-containing enzymes are readily inactivated by relatively small doses of radiation (22).

Vermund and Stenstrom (22) have shown that radiation inhibits the synthesis of deoxyribonucleic acid (DNA) which is necessary for cell reproduction. DNA has been considered to be the stable major constituent of the genes, which carry the hereditary characteristics. DNA is in high concentration in rapidly proliferating tumors. Radiation appears to inactivate certain sensitive enzymes, and through these DNA formation is inhibited.

Vermund and Stenstrom (22) also believe that radiation effects on the normal tissues of the tumor bed may favorably effect regression of the tumor. According to Ewing, radiation affects the small capillaries of the tumor and thus deprives the tumor cells of adequate nutrition. It is known that irradiation of a tumor *in vitro* with subsequent implantation requires much higher doses to inhibit growth than when the tumor is irradiated *in vivo*. Thus the effects of radiation on the tumor bed must contribute to the total effect on the tumor. Difference of opinion exists only regarding the relative importance of the effect of radiation on the tumor bed.

Vermund and Stenstrom (22) obtained experimental data showing prevention or significant retardation of the growth of tumors transplanted into areas which had received radiation in a dosage of 1500 roentgens in air forty-eight hours beforehand. When they re-transplanted a tumor that had been growing slowly in a previously radiated area, into a normal area, the result was re-establishment of the tumor's natural growth. Thus tumor cells retain their natural potentialities for growth in spite of temporary sojourn in radiated tissues.

III. CHANGING THE RESPONSE TO RADIATION BY ALTERING THE CHEMICAL PATTERN IN A TUMOR

It is evident from what has been stated that the biologic action of ionizing radiation on cells and tissues is very complex. It is thought that the biologic effects are the result of changes which take place in living cells, and that indirect effects may be caused by radiation-induced chemical fragments which enter into reactions to form new compounds. In this way the chemical pattern inside a tumor may be altered. Attempts have been made to increase radiation effects by the addition of substances, either before or during radiation.

Tumor cells are generally more anoxic than the normal tissues around them. As the oxygen concentration to which cells are exposed is increased, there is a definite increase in radiosensitivity. Thus a tumor, since it is relatively anoxic, occupies a lower position in the radiosensitivity curve than does normal well vascularized tissue. Therefore, it might be possible to increase tumor radio-

sensitivity relative to that of normal tissue by subjecting the whole animal to increased oxygen tension.

Conger (23) used Ehrlich's mouse ascites tumor cells which were equilibrated with atmospheres of various oxygen concentrations. After irradiation, fresh mice were inoculated with the fluid; samples drawn by peritoneal puncture were then examined periodically. The author found that if the sensitivity of cells under anoxic conditions were considered as unity, the sensitivity increased about three-fold when subjected to 21 per cent oxygen (air). Any further increase in oxygen tension caused little increase in sensitivity. Conger stated that an overall elevation in oxygen tension of the whole organism, induced by breathing pure oxygen, would increase the radiosensitivity of both normal and tumor tissue.

It has long been known that ionizing radiation acts in two ways: 1) the deleterious effect on cells, partly caused by the action on sensitive cell elements, and 2) the damage caused by the intermediate split products of the irradiated water which makes up the major part of the cells (24). These split products, which appear to be unstable, are the result of the action of strong oxidizing radicals, the formation of which is appreciably increased in the presence of oxygen. The maximum effect on radiosensitivity found experimentally by increasing the oxygen tension was a three-fold increase.

The percentage increase in biologic effect on the tumor is high when comparison is made between zero oxygen concentration and a concentration similar to that found in normal healthy cells. A further increase in oxygen supply above the value found in healthy cells does not cause appreciable increased damage to the tumor.

Tumors in general are characterized by anaerobic metabolism associated with a low oxygen concentration in the tumor cells. If the oxygen concentration could be raised experimentally, damage to the tumor by radiation could be appreciably increased, whereas damage to the surrounding tissue would be only slightly increased. Gray *et al.* (25) showed that this is possible in mice with Ehrlich's ascites tumor by having the animals breathe pure oxygen shortly before, and during irradiation of the inoculated tumors. They also found that old tumors responded less favorably to this treatment, as the oxygen could not reach the tumor cell because of a disordered vascular system.

Hultborn and Forssberg (26) compared the effect of inhalations of pure oxygen in 4 patients with skin tumors which were irradiated. The effect of radiation was noted both on the tumor and on the surrounding normal skin. In each case, the skin cancer was divided into two fields—one irradiated during inhalation of oxygen, and one irradiated without such inhalation. In a patient who had multiple carcinomata, some of the growths were treated during inhalation of oxygen, and some when no oxygen was being inhaled. In all the cases the authors felt that inhalation of oxygen amplified the effects of radiation in the tumor tissue, without having appreciably increased the effects on the surrounding normal skin.

Schwartz *et al.* (27) found that hematoporphyrin tends to become localized in some types of human and animal cancer (27). In man, intravenous doses appear

to reinforce the effects of roentgen or gamma irradiation in some tumors previously found to be resistant because of their nature and size. Many activities of porphyrin resemble those of ionizing radiation. Both denature proteins, both cause oxidative reactions, both are associated with release of histamine, both have carcinogenic properties. In addition, the metabolism of porphyrin enzymes in tumors may modify the effect of radiation, because porphyrin enzymes play a major part in tissue oxidation, and the oxidative status of tissue is important in determining the response to radiation.

In one group, Schwartz *et al.* noted that porphyrin increased the radiation effect in the majority of patients (27). In another group, having neoplasms ordinarily refractory to x-rays, there was at least 50 per cent regression in the first two or three weeks of therapy. In the other groups the effects were not clear-cut. The results suggest that hematoporphyrin enhances the action of roentgen rays in some human cancers, but not in others. When successful, the tumor response was often surprisingly prompt; occasionally the reduction in size of the tumor began after three to seven days of therapy. This was especially remarkable in a case of suspected tumor resistance to x-ray therapy.

IV. THE HAZARDS OF RADIATION

There is common agreement among radiation scientists that any amount of radiation, however small, is capable of doing some harm. Recently there have been marked differences of opinion among atomic scientists relative to the actual danger of radioactive fall-out resulting from atomic blasts. Medical usage is estimated to be the largest man-made source, creating an amount of radiation exceeding by far, that of radioactive fall-out in atomic bomb testing and in all the peaceful uses of atomic energy.

The value of radiology in the service of medicine is immeasurable and can be considered as one of the greatest single contributions to clinical medicine. Since the practice of medicine had become increasingly complex, more and more reliance is being placed on radiography in diagnosis. The radiologist has learned through bitter experience the danger of overexposure to radiation. However, the neophyte with a fluoroscope, often examining the patient without taking pains to accommodate his vision to the image on the screen, may be the unwitting cause of overexposure. Pediatricians especially, in their monthly check-ups of well babies, often use the fluoroscope. When the mother is also in the fluoroscopy room and asks to have each finding explained, minutes may elapse and the child may be overexposed. Then there are patients who go from clinic to clinic and from hospital to hospital seeking an elusive diagnosis, and in the process absorbing a tremendous amount of radiation. Repeated dental x-ray examinations may in certain instances also present a hazard. There have been several published reports on the relation of radiation to subsequent thyroid cancer and leukemia. Therefore, it behooves all physicians to restrict diagnostic radiation to those patients who actually can profit from its use.

Although it cannot be stated definitely that there is a direct relationship between neoplastic disease and overexposure to radiation, the association appears

often enough to justify extreme care. Irradiation of enlarged thymus in infants was first introduced by Friedlander (28) in 1907, and since then has become widely practiced in this country. Duffy and Fitzgerald (29) reported 28 cases of thyroid cancer in children under 18 years of age; among these, 9 had been given x-ray therapy for an enlarged thymus within the first twelve or eighteen months of life. Simpson *et al.* (30) studied the case histories of 1400 children who had received x-ray therapy to the thymus in the period 1925 to 1951. In 17 of these children malignant neoplastic disease had developed, chiefly carcinoma of the thyroid and leukemia; 9 others had an adenoma of the thyroid. An equal number of controls were also studied, and the results indicated that the incidence of neoplastic disease was significantly higher in the radiated group.

Clark (31) reported on 15 children with thyroid carcinoma, all of whom had been treated with x-ray therapy for benign conditions. The total dose used ranged from 200 r to 725 r. He stated that the increasing incidence of carcinoma of the thyroid in children and adults seems to be correlated with the widespread use of x-ray therapy for benign conditions of the head, neck and chest (including the thymus).

It appeared clear to Dameshek (32) that of the various etiologic factors proposed for human leukemia, the only certain one is exposure to radiation. For example, the incidence of leukemia in radiologists is eight to ten times higher than among physicians in other specialties (33); a relatively high incidence of leukemia has been reported in England and Holland in patients treated for spondylitis with x-ray therapy (34); there is a comparatively high incidence of leukemia in patients treated for enlarged thymus by x-rays (30); and well known is the high incidence of leukemia in survivors of the atom bomb blasts of Hiroshima and Nagasaki (35), especially near the hypocenters. The increased use of x-rays for determining fetal size and position has been suggested as a cause (36). Animal experimentation has also shown the leukemogenic effect of ionizing radiation (37).

Because of the possible relationship between malignant neoplastic disease and previous diagnostic and therapeutic radiation, a set of rules has been proposed which should prove helpful in reducing the danger (38):

1. The appointment of committees to evaluate and limit the use of x-ray therapy for dermatologic diseases, bursitis, rheumatoid spondylitis and enlarged thymus.
2. Limitation of the use of diagnostic x-ray procedures to those expected to provide essential information.
3. Possession by the patient of a radiation diary in which there is a permanent record of his x-ray dosage of both diagnostic and therapeutic radiation.

Although the genetic effect of radiation has been the one most widely discussed, other effects are also exceedingly important, *e.g.*, induction of cancer and leukemia, reduction of the life span, and the development of an acute radiation syndrome.

It is stated that the amount of radiation which will kill half of the population in thirty days is about 400 r to 450 r of general body radiation. About 150 r of

general body radiation will produce unequivocal symptoms. The acute radiation syndrome is a fairly typical picture, as noted in the Hiroshima bomb cases and in a few cases of radiation accidents (39) (Table 1).

The life span of small animals can be shortened significantly by 300 r of general body irradiation. In line with this finding, radiologists have a life expectancy which is five years less than that of physicians without contact with radiation. Although this decrease in the life span is due in part to an increased incidence of cancer and leukemia in radiologists, the predominant effect is merely an intensification of the normal process of aging.

Rall (40) gives a table showing the amount of radiation that may accompany certain diagnostic and therapeutic procedures, as well as the amount of fallout from atomic testing. The danger from diagnostic and therapeutic radiation is at present much more than from atomic bomb tests. For example, the "permissible" amount of radiation per year is about 15.6 r. General background radiation per year amounts to .2 r, and the atomic fallout in 1954 was 0.015 r. A chest roentgenogram produces .1 r, and two-minute fluoroscopy produces 34.0 r. He warns that 6 or 8 fluoroscopic examinations of two or three minutes each may deliver a total dose of 400 r to a large part of the abdomen. This amount could probably reduce this person's life span, and if the patient were female, would certainly cause genetic damage. Rall also cautions that a female in the child-bearing age

TABLE 1

The Acute Radiation Syndrome

	Lethal Dose	Median Lethal Dose	Moderate Dose
	(600 r)	*(400 r)*	*(100–300 r)*
First week	Nausea and vomiting after 1–2 hours	Nausea and vomiting after 1–2 hours	
	No definite symptoms	No definite symptoms	No definite symptoms
Second week	Diarrhea, vomiting, inflammation of mouth and throat	Beginning epilation, anorexia and general malaise, fever, inflammation of mouth and throat, anemia, petechiae, internal bleeding,	
Third week	Fever, emaciation, death (probably 100% mortality)		Epilation, anorexia, general malaise, diarrhea, petechiae, anemia, emaciation, recovery (unless complicated by injury or infection)
Fourth week		diarrhea, emaciation, death (mortality about 50%)	

should be considered pregnant for two weeks before her menstrual period, and made a plea for postponing diagnostic x-ray examination until just after menstruation.

Rall (40), in an interesting report on the radiation problem, stated that if a 100-r dose of radiation be delivered to an ovary of a woman prior to reproduction, there will be 1 chance in 2 of a mutation in the child. The chance of this mutation developing in the first generation is approximately 1 in 200. He further stated that if each person in the United States, prior to reproduction, had a fluoroscopic examination which resulted in a dose of 5 r to the gonads, and if the population in the reproduction period numbered 40,000,000, this amount of radiation would cause 500,000 mutations. It has been shown in certain species, and is also apparently true of humans, that almost all mutations are deleterious. In Drosophila, even mutations involving such trivial characteristics as color of the eyes and shape of the wings, lessen strength and shorten the life of the fly bearing the mutation.

There has been much controversy about the danger of radiation from the testing of atomic weapons (41). About 5 per cent of the debris from an atomic bomb is krypton^{90}, a gas which rises rapidly from the explosion site and flows high into the stratosphere for from four to seven years before returning to the earth. Krypton^{90} decays quickly into strontium^{90}, which has a half-life of twenty-eight years and then decays into yttrium^{90}, which has a half-life of sixty-five days. Yttrium^{90} has the most powerful beta radiation of all three members of this family. Strontium^{90} and yttrium^{90} together bombard the soil, plants, milk and bones; they travel along with calcium. Cesium^{137}, also a result of atomic bomb debris or fall-out, has a half-life of thirty-three years. It enters muscle as well as milk, so that eating meat which may contain it will expose the eater to internal radiation.

It has been stressed by Libby (42) of the Atomic Energy Commission that natural background radiation (for example, from cosmic rays and natural radioactive materials in the environment) is a greater threat than radioactive fall-out from atom-bomb blasts. He states that the permissible amount of strontium^{90} for atomic-energy workers in the United States is about 2000 times the present strontium^{90} content of new bone in the United States resulting from radioactive fall-out. Authoritative groups have recommended that the permissible limit for whole populations should be one-tenth that of atomic-energy workers. On the basis of these calculations, Libby concludes that the present level in new bone—*i.e.*, in children in the United States—is less than 1 per cent of the maximum permissible concentration for the population.

Strontium^{90}, because it is concentrated in bone, probably does not irradiate the sex organs. Radioactive fall-out includes other materials with penetrating radiation which can irradiate the sex organs and thus can produce genetic mutations. Libby states that external fall-out radiation is only from 0.7 to 3.0 per cent of that from natural sources, and that the genetic effect of fall-out radiation must be very small compared to that of natural radiation.

On the other hand E. B. Lewis (43) of the California Institute of Technology

believes that the incidence of leukemia is increased by exposure to low dosage radiation. In a statistical study, Lewis found that a substantial number (above 20 per cent) of cases of leukemia are induced by the natural radiation which we receive constantly, *e.g.*, cosmic rays, radioactive elements in rocks, bricks and concrete, radioactive gas in the atmosphere, and radioactivity in our bones. There is no threshold of radiation dosage below which leukemia does not appear. Thus each small amount of radiation received by any individual increases by a calculable amount the possibility that he may die from leukemia. Lewis states that there would be a 5 to 10 per cent increase in the current spontaneous incidence of leukemia if the population were to reach and maintain a body level of strontium^{90} amounting to one-tenth of the maximum permissible concentration. Harrison Brown (44), commenting on the study, states, "Continued testing at the present rate may well result in the death each year from leukemia of nearly 10,000 persons who would otherwise not have died."

Any amount of radiation, however small, can do some harm. It is therefore incumbent on us as physicians to hold all forms of radiation to the lowest possible level. As citizens, moreover, we must know that the hazard of weapons testing and of nuclear reactors for power production is also great, and will increase as the years go by. In the words of Graham DuShane (45), editor of *Science*, "It is apparent that the atomic dice are loaded. The percentages are against us, and we ought not to play unless we must to assure other victories."

An important principle has been brought out in a recent article by Crossland (46) on the use of x-ray therapy in dermatologic practice. He stated that this is a time for caution but not for panic or fear of the unknown; and that, although careless or casual use of radiation is to be condemned at any age, even the hazards of this nuclear age are not sufficient to warrant withholding radiation therapy from those who need it. With these points we must agree; but with the added caution that we must utilize all other effective therapy before deciding that radiation is necessary. The crux of the problem, we feel, is that each roentgen should be doled out, and when other effective therapy is available, it should be used in preference to radiation.

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APPENDIX

Definition of units used for measuring ionizing radiation (47):

X-rays or gamma (γ)-rays do not ionize directly, but they may impart all or part of their energy to electrons met in their path, and these electrons (the "associated corpuscular emission" in the definition of the roentgen given below) then cause ionization.

Roentgen—This unit of radiation dosage (r) is defined as a quantity of x or γ radiation such that the associated corpuscular emission per 0.001293 gram of air (actually the weight of 1 cc. of air at normal temperature and pressure) produces in air, ions carrying 1 electrostatic unit of quantity of electricity of either sign.

Rad—The rad measures the energy deposited by radiation per unit mass, rather than the ionizing effect. An approximate relation to a roentgen is expressed by the fact that 1 roentgen absorbed in tissue = 0.95 rad.

Curie—The curie is a measure of the number of atoms of a radioactive substance which disintegrate every second. If the energy of the particle or the radiations emitted from a radioactive substance be known, one can compute the dose in roentgens delivered by a given radioactive source. For example, for the γ rays from radiocobalt—1 curie produces a dose of 1.3 roentgens per hour at a distance of 1 meter.

Abstracts of Current Literature

GERIATRIC ANESTHESIA.

Ausherman, H. M. *M. Times*, New York **85:** 1363 (Dec.) 1957.

The problem of anesthesia in the aged is that of choosing the least harmful agent and technic to fulfill the requirement for surgery in a given patient. However, the skill of the anesthesiologist is the most important in securing successful anesthesia in the aged. The anesthesiologist is particularly concerned with understanding the anatomic and physiologic changes that have taken place during aging in the cardiovascular, respiratory and excretory systems. Other changes that contribute to a decreased reserve under stress in elderly people include nutritional deficiencies, increased protein requirements, and impaired carbohydrate metabolism. In order to make a careful evaluation of the patient, the anesthesiologist should review the complete physical examination. Laboratory examinations should include an electrocardiogram, uninalysis, complete blood count, and a roentgenogram of the chest. Preoperative medication should be held to a minimum. Barbiturates and scopolamine are not well tolerated by elderly persons. Atropine is superior in this respect. Demerol has a more favorable action than opiates in the aged because the degree of depression is less and its effect more predictable. Supportive therapy preoperatively should include hydration and blood replacement, nutritional replacement and vitamin supplementation, regulation of the cardiac reserve, and the administration of antibiotics, if necessary. The chosen anesthetic agent should provide safety and comfort for the patient, satisfactory relaxation and operating conditions for the surgeon, and convenience for the anesthesiologist. Spinal anesthesia may be excellent in the aged provided certain precautions are observed. Spinal analgesia must not be allowed to rise above the tenth dorsal vertebra because of the danger of a drop in blood pressure accompanied by coronary and cerebral hypoxia and decreased tidal gaseous exchange. Some procedures that can be performed under spinal anesthesia are hip nailing, lower abdominal surgery, rectal or perineal surgery, surgery of the lower extremities, vaginal hysterectomy, and prostatectomy. The combination of mild analgesia with hypnosis by means of nitrous oxide or ethylene with oxygen, or small doses of an ultrashort-acting barbiturate like Pentothal or Surital, makes the procedure more acceptable to the patient. Any of the volatile agents and technics or ultrashort-acting drugs administered intravenously for general anesthesia can be used in elderly patients. They must, however, be used in smaller amounts and with great care and skill because the margin of safety is less in these patients than in those who are younger. The plan outlined for use during anesthesia and surgery includes adequate oxygenation, a minimum amount of anesthetic agent, replacement of blood as lost, a stable blood pressure, short duration of surgery, and the avoidance of a radical position. When general anesthesia is used, its induction should be smooth, a light even plane of anesthesia maintained, nonirritating drugs administered, and rapid recovery from anesthesia afforded. Postoperative management requires frequent moving, early ambulation, scrupulous care of the respiratory tract, avoidance of oversedation, and careful nursing.

ANALGESIC EFFECTIVENESS OF ORALLY ADMINISTERED ETHOHEPTAZINE IN MAN.

Batterman, R. C.; Golbey M.; Grossman A. J., and Leifer, P. *Am. J. M. Sc.* **234:** 413 (Oct.) 1957.

Ethoheptazine, a new analgesic with a seven-membered cyclic ring structure, fills to a high degree the need for a moderately potent oral analgesic. Satisfactory analgesia, regardless of etiology of the painful state, was achieved with 200 mg. daily in divided doses in 73

per cent of ambulatory patients (aged 16 to 80 years), most of whom had musculo-skeletal complaints. Although the presence of an inflammatory exudative process limits the value of a purely analgesic drug, satisfactory analgesia was obtained in the majority of the patients with rheumatoid arthritis. Most of the patients with gastro-intestinal, cardiac, and renal diseases also responded. In hospitalized patients, a dosage of 50 mg. four times daily proved inadequate; 100 mg. orally at the same intervals furnished satisfactory analgesia in 62 per cent of the trials in 105 hospitalized patients (aged 18 to 92 years). Again, the greatest effectiveness was in the relief of musculo-skeletal pain. In early neoplastic disease, when the pain did not require potent injectable analgesics, 50 per cent of patients had satisfactory analgesia. In severe pain, when morphine or meperidine ordinarily would be required, ethoheptazine was ineffective, regardless of the condition present. In renal disease and myocardial infarction, no effective relief of pain was obtained. Headaches failed to respond. Analgesia was satisfactory in neurologic patients with neuritis or tabes dorsalis, and in postoperative or surgical patients with mild pain. Untoward reactions occurred in 4 per cent of both ambulatory and hospital patients. These consisted of anorexia, nausea, and dizziness. The combination of ethoheptazine with aspirin enhanced the likelihood of achieving satisfactory analgesia. Thus the response of rheumatoid arthritis patients was superior to that of patients who received ethoheptazine alone. The combination caused a 12 per cent incidence of side-actions consisting of nausea, epigastric burning, and headache. Postpartum pain was satisfactorily controlled in 82 per cent of patients treated with ethoheptazine alone, and in every patient treated with this drug in combination with aspirin. Prolonged administration of ethoheptazine in ambulatory and hospital patients proved to be safe. In these studies no tolerance or physical dependence could be demonstrated.

ZUR LOKALEN APPLIKATION VON ULTRACORTENOL IN DER AUGENHEILKUNDE (LOCAL APPLICATION OF PREDNISOLONE IN OPHTHALMOLOGY).

Cagianut, B. *Praxis* **46:** 660, 1957; through Ciba Literature Review **2:** 283 (Sept.) 1957.

Local application of sparingly soluble corticosteroids marks a substantial step forward in ophthalmologic treatment, since in this way a disease of limited extent can be controlled without fear of an effect being exerted upon the body as a whole. Ultracortenol (prednisolone trimethylacetate) has proved particularly effective in numerous cases. The following groups of diseases have been treated with Ultracortenol in the form of ointment (0.5 per cent) or drops (0.3 per cent): bacterial infections (in combination with antibiotics), chronic or peracute bacterial inflammation, inflammatory processes caused by viruses, aseptic inflammation of traumatic origin, "overshooting" allergic and immunity reactions, and primary and secondary degeneration of optical important media. The response was particularly good in cases of severe bacterial inflammation of the cornea and conjunctiva—in which Ultracortenol proved distinctly superior to hydrocortisone—as well as in allergic eye diseases and inflammation of the anterior chamber. The more acute the process, the better the prospects of success appeared to be. The results were unsatisfactory in inflammation of the posterior segment of the eye and in degenerative processes. Ultracortenol was well tolerated, even after prolonged use. When treatment was continued for an adequate period of time, relapses seldom occurred.

ÉTAT ACTUAL DU TRAITEMENT DES CIRRHOSES ASCITIQUES PAR LA DELTACORTISONE (STATUS OF TREATMENT OF CIRRHOSIS WITH ASCITES BY DELTACORTISONE).

Cattan, R., and Vesin, P. *Semaine d. hôp. Paris* **33:** 76, 1957; through Ciba Literature Review **2:** 280 (Sept.) 1957.

Thirty-two patients with cirrhosis of the liver and ascites received prednisone initially in a daily oral dosage of 30 to 40 mg., along with a diet rich in protein and moderately poor in salt. After the third day, the dosage was reduced to 20 mg. No further punctures of the ascites were performed. Fourteen patients responded well. The ascites disappeared com-

pletely during prednisone treatment and did not return even after discontinuation of the drug. The appetite and general condition improved. The blood protein level often rose as much as 10 per cent. In 4 patients, the ascites persisted to a certain extent or returned after completion of the treatment. In the remaining 14 patients, the excretion of urine sometimes increased initially but, in general, the results were unsatisfactory. In cases with a good response, diuresis commenced about the third or fourth day, and rarely about the eighth day. The excretion of urine in amounts of 3 liters or more in twenty-four hours was not accompanied by increased thirst. In patients in whom the treatment was permanently successful, large quantities of sodium were also excreted, with the result that the sodium balance became strongly negative. Symptoms of sodium deficiency, however, did not appear. This excretion of sodium is related to the inhibition by prednisone of the secretion of sodium-retaining aldosterone in the adrenal cortex.

TWO YEARS' EXPERIENCE WITH PREDNISONE IN RHEUMATOID ARTHRITIS.

Fearnley G. R.; Balmforth G. V., and Blatchley, R. *Brit. M. J.* **2:** 1263 (Nov. 30) 1957.

Among 167 patients with moderate or severe rheumatoid arthritis, 15 were treated initially with prednisone. After two years, 47 were being treated with prednisone, 16 having been transferred from aspirin, 8 from phenylbutazone, and 8 from cortisone because of the failure of these drugs. The majority of the patients were over age 40 years and some over age 70 years. With increasing experience in the use of prednisone, the tendency was to use it earlier, often without the previous trial of aspirin, and to be less strict in the criteria for its administration. Forty-two patients are still receiving prednisone. It was discontinued in 2 patients because of a spontaneous remission at six and eight months, respectively, and in 3 patients because of side-actions. The initial dosage was 5 mg. every eight hours. In 8 patients, it was possible to reduce to a maintenance dosage of 2.5 mg. at the same intervals. Large doses were not used because it was thought that some of the initial dramatic improvement might be lost as the dose was reduced in the presence of depression of the patient's adrenal glands. Functional status improved in 50 per cent of the patients given prednisone. Subjective improvement was reported by 90 per cent. According to the patients' evaluation, 43 believed themselves improved by treatment with prednisone. Mild and transient dyspepsia occurred in 4 patients. Five others required an antacid for the control of dyspepsia but no ulcer could be demonstrated roentgenographically. Antacid was not given routinely and was administered separately to patients having dyspeptic symptoms. Prednisone was withdrawn from 1 patient with an active duodenal ulcer. A prepyloric ulcer developed in 1 other patient but healed during the continued administration of the steroid together with an ulcer regimen. An elevation in blood pressure forced the discontinuation of the steroid in 1 patient. Diabetes developed in 1 patient after two months of prednisone, and the insulin requirement in a known diabetic patient had to be increased. Pronounced obesity occurred in 4 patients. Prednisone had to be discontinued in a woman with a history of nervous breakdown because of agitation and depression. Agitation, tiredness, and generalized weakness in another patient subsided as prednisone was continued. It is concluded that prednisone affords substantial relief in the large proportion of patients with rheumatoid arthritis. The relief appears to be satisfactorily maintained, so far, in the patient studied. At present, the benefit to be obtained from this therapy outweighs the risks and complications attendant upon administration of prednisone. The risk is deemed justified in the case of the wage earner on the point of incapacity, the housewife unable to care for a young family, and the patient who is deteriorating rapidly despite other therapy.

THE INFLUENCE OF GONADAL HORMONES ON SERUM LIPIDS AND LIPOPROTEINS: STUDIES IN NORMAL AND HYPOGONADAL SUBJECTS.

Furman, R. H., and Howard, R. P. *Ann. Int. Med.* **47:** 969 (Nov.) 1957.

From two studies, one in 60 normal and hypogonadal men and women and one in 24 eunuchs and 20 noncastrates, it is concluded that the serum level of high-density (alpha)

lipoproteins and the ratio of high-density to lower-density (alpha/beta) lipoproteins are sensitive indicators of change in gonadal hormone relationships. An increase in relative estrogenicity, whether by administering estrogen or withdrawing androgen, is always associated with an increase in high-density lipoprotein concentrations and high-density/low-density lipoprotein ratios. An increase in relative androgenicity has the opposite effect. The lower-density (beta) lipoprotein response is more variable but usually opposite to that of the high-density fraction. Changes in chemically determined cholesterol and phospholipid levels appear to be determined by the nature of the changes in the major lipoprotein fractions under these conditions. On the other hand, absence of change in serum cholesterol or phospholipid levels does not preclude the possibility of major alteration of the lipoprotein spectrum. Whether these serum lipoprotein-hormone relationships are causally related to the marked sex difference in the incidence of coronary artery disease remains to be determined by further study. There is good agreement among workers in this field that the concentration and physical status of the serum lipids have some etiologic significance in this disease. Therefore, further efforts in the direction of the studies described are warranted. (From authors' summary and conclusions.)

LE TRAITEMENT DIÉTÉTIQUE DE LA CIRRHOSE HÉPATIQUE. SES LIMITES ET SES DANGERS (DIETETIC TREATMENT OF HEPATIC CIRRHOSIS. ITS LIMITS AND DANGERS).

Gajdos, A. *Presse méd.* **65:** 1249, 1957; through Ciba Literature Review **2:** 282 (Sept.) 1957.

The administration of a diet rich in protein and poor in salt to patients with cirrhosis of the liver is an advance over former dietary prescriptions. The absorption of ascites is facilitated and the patient's life appears to be prolonged. There are, however, an increasing number of reports to the effect that a protein-rich diet is by no means harmless for the cirrhotic patient, that it may lead to neurologic and psychic disorders, and may promote the onset of hepatic coma. This harmful effect is probably due to the accumulation of ammonia in the body (especially in the central nervous system) or to a disturbance in protein metabolism. Good results were obtained with a varied diet which provides the cirrhotic patient with 3,000 to 3,500 calories daily and contained 80 to 100 Gm. of protein, 350 to 400 Gm. of carbohydrate, and 100 to 150 Gm. of fat. This quantity of protein is adequate in cases of compensated cirrhosis. When cirrhosis is severe, it helps to prevent an aggravation of the anorexia and the appearance of neurologic complications. The dangers of salt withdrawal must also be borne in mind. For only a short time should the diet contain no sodium chloride. As soon as the diuretic crisis commences, or (if it fails to occur) as soon as the sodium level drops, it is advisable to give 3 to 4 Gm. of table salt daily.

TREATMENT OF DIGITALIS TOXICITY BY CHELATION OF SERUM CALCIUM.

Gubner, R. S., and Kallman, H. *Am. J. M. Sc.* **234:** 136 (Aug.) 1957.

Arrhythmias due to digitalis toxicity were terminated promptly in 3 patients by intravenous infusion of the disodium salt of ethylene-diamine tetra-acetic acid, a chelating agent which binds and inactivates serum calcium. In 2 other patients, prior administration of the disodium salt of EDTA in one, and the magnesium salt of EDTA in another, significantly increased the dose of digitalis glycosides required to produce major arrhythmias. The use of EDTA in the treatment of digitalis toxicity is predicated on the synergistic relationship between digitalis and calcium. It appears probable that their effects on cardiac rhythmicity are mediated via their action at the myocardial cell membrane, determining permeability to potassium. Digitalis and calcium promote potassium loss from the myocardium thereby increasing irritability. The use of EDTA offers certain advantages over potassium administration in treating digitalis toxicity. Its action is very prompt and is safer than intravenous potassium. Oral potassium is slow in effect and large doses are required which may not be well tolerated. EDTA is effective in abolishing both atrial and

ventricular ectopic rhythms caused by digitalis. In certain instances atrial arrhythmias produced by digitalis may mimic ventricular extrasystoles and ventricular tachycardia due to accompanying functional bundle branch block. It is important that arrhythmias due to digitalis toxicity be controlled promptly in patients with heart failure, for apart from the classic hazard of ventricular fibrillation, heart failure may be paradoxically aggravated by digitalis when arrhythmias are produced by overdosage. (Author's summary and conclusions.)

IL PRURITO ANALE. RILIEVI CLINICI SULL'IMPIEGO TERAPEUTICO DEGLI ESTRATTI DELLA RAUWOLFIA SERPENTINA BENTH. (ANAL PRURITUS. CLINICAL RESULTS OF TREATMENT WITH RAUWOLFIA SERPENTINA).

Jannarone, G. *Gazz. med. ital.* **116:** 79, 1957; through Ciba Literature Review **2:** 276 (Sept.) 1957.

In the treatment of pruritus ani it is important to eliminate local factors such as hemorrhoids, rhagades and *Oxyuris*, which may be involved in the pathogenesis of the condition. In addition, diabetes, infectious or parasitic colitis, and anemia must be properly treated as they, too, may account for the appearance of anal pruritus. Patients who fail to respond to any form of local or general treatment are frequently of the anxious or neurotic type. Thirteen such cases of refractory pruritus ani were treated with Serpasil in daily oral doses up to 3 mg. A good response was obtained. Serpasil not only produced tranquillization but in almost every case improved the patient's general condition and relieved insomnia. Simultaneously, the lesions regressed. In a typical case, a 54-year-old man with violent pruritus ani of eight years' duration, which had failed to respond to any treatment, had lost considerable weight and was in a state of psychomotor excitation. Soon after Serpasil therapy was begun, the pruritus subsided, the patient's general condition improved, and his appetite increased. He became calmer and more confident. After treatment for thirteen weeks, he no longer complained of itching. This benefit had been maintained at the time of re-examination several months later.

METRAZOL FOR CENTRAL NERVOUS SYSTEM ARTERIOSCLEROSIS IN AGING PATIENTS.

Kapernick, J. A. *Geriatrics* **12:** 703 (Dec.) 1957.

Metrazol was administered to 687 patients aged 58 to 83 years with clinically diagnosed cerebral arteriosclerosis, each of whom was observed for an average of two and one-half years. Approximately one-third of the patients gave a history of small strokes or were known to have had them, and 10 per cent had primary psychiatric disorders including deliria, confusional states, or agitated behavior with dementia and delusions. Many were disabled by insecurity, weakness, and varying degrees of withdrawal. No patient was accepted who had severe hypertension, severe or poorly controlled diabetes, lues or a history of treatment for lues, or a history of severe head injury. An attempt was made to rule out the presence of chronic subdural hematoma and brain tumor. Metrazol was given to cooperative patients in doses of 4.5 to 12 gr. daily. Noncooperative patients initially received up to 80 gr. daily by injection. Oral medication was instituted as soon as practicable in an average dosage of 9 gr. daily. The response to Metrazol was judged by observation of the patient, the patients' reports of improvement, the reports of family members, the patients' responses to placebo medication, willingness to continue medication, and objective performance as related to such factors as resumption of employment, willingness to travel, and care in dress. In patients with psychiatric disorders, recovery from overt behavior problems and social adjustment were evaluated. Eighty-four per cent of the patients showed a good to excellent response. Improvement consisted of increased activity, better sleep pattern, social adaptability, subjective feeling of well-being, freedom from symptoms, and lessening of disability. Twelve per cent showed no evidence of significant improvement. In an additional 4 per cent, the drug was considered to have failed because the patients were unable to tolerate Metrazol, were indifferent to dosage schedules, were willing to

discontinue the drug, or had a favorable response to placebo medication. No toxic reactions nor seizures, and few side-actions, were seen. However, patients with a familial history of epilepsy, or in whom electroencephalographic examination indicates focal abnormalities, should be cautioned that an occasional seizure may occur. It is concluded that Metrazol is a safe and useful adjunct in the treatment of elderly persons with arteriosclerotic disease of the central nervous system.

TREATMENT OF TUBERCULOSIS IN THE AGED.
Kinsella, T. J. *Minnesota Med.* **40:** 766 (Nov.) 1957.

Today the average patient entering a sanatorium with active tuberculosis is an elderly male whose disease has been discovered by roentgenograms of the chest made, for example, in a city jail, a general hospital, a rest home, or a home for the aged. Tuberculosis in the elderly is now known not to be a slow chronic process; persons well advanced in years may have primary acute lesions. The diagnosis frequently may be missed because of past disease or previous diagnosis of associated conditions which may simulate, mask, or obscure the tuberculous process. Groups that bear careful scrutiny because of an increased incidence of tuberculosis among them include those with diabetes, alcoholism, silicosis, the mentally disturbed, those receiving cortisone, and some who have had extensive gastric resection. Adequate treatment is essentially the same as that in younger persons, with modifications to suit the needs and meet the limitations of elderly persons. Such treatment consists essentially of isolation, a modified rest program, specific antituberculosis therapy, a complete study of the patient, and evaluation as to the necessity for surgical therapy. Drug therapy may be intensive and prolonged, but adaptations will be required in accordance with the patient's condition. For example, one with emaciated gluteal muscles may not tolerate repeated injections of streptomycin, and one with a poor appetite and digestive disturbances will be a poor candidate for large doses of certain medications. A careful and complete study of the patient by physical examination, laboratory studies, electrocardiographic examinations, and roentgenographic examinations is essential to management. It furnishes a basis for estimating the patient's ability to withstand any contemplated additional procedures. Among surgical procedures that may be used to advantage in elderly persons with tuberculosis that does not clear completely with conservative measures plus chemotherapy, are pneumothorax, thoracoplasty, and extrapleural or estraperiosteal plombage. Even if some of these are not successful, they may serve as preparation for subsequent resection should that become necessary. Resection of residual significant cavitary or symptom-producing disease is possible but requires caution and the establishment of certain limits, as the procedure is more hazardous in older persons than major surgery to the abdomen, for example. Kinsella performed resection on 124 patients past 50 years of age (2 of whom were past 75 years of age) with an operative mortality of 2.4 per cent. No more frequent complications were encountered than in a total resection series. The complications were related more to bacterial resistance than to the age of the patient or his disability. Surgical excision should be aimed at the removal of significant residual conditions, caseous abscesses, open or inspissated cavities, and symptom-producing bronchiectatic areas, that is, all symptom-producing and bacteria-dispensing lesions, so that the patient is no longer infectious and can return to normal living conditions. The care of these patients demands that cyanosis be avoided, oxygen be used frequently, fluctuations in blood pressure be avoided, the legs be wrapped, and active motion of the lower extremities carried out in an attempt to prevent venous stasis, thrombosis, and embolic phenomena. Much can be accomplished in the elderly patient with tuberculosis by use of the plan of management outlined.

PSYCHIATRIC AND PSYCHOLOGICAL OBSERVATIONS IN A GERIATRIC CLINIC.
Kral, V. A. and Wigdor, B. T. *Canad. Psychiat. A. J.* **2:** 185 (Oct.) 1957.

Forty-seven patients seen during the first ten months of operation of a geriatric clinic were examined medically, psychiatrically, and neurologically. Psychologic testing was

carried out in 42 persons, of whom 27 were women and 15 men. The technics used were the Wechsler-Bellevue Intelligence Scale I, the Rorschach Test, and the Bender-Gestalt Visual Motor Test. A low I.Q. and low E.Q. were found for the group as a whole. This was thought to be due in part to the lifelong low socioeconomic status of the patients, but more to the fact that this was an organically impaired group. Of those tested, 59.5 per cent showed clear signs of organic impairment in the psychologic tests, although only 19 per cent presented the clinical picture of organic brain disease. This was interpreted to indicate a capacity to compensate for organic deficits even at an advanced age. It is suggested that "personal factors," which may be physiologic, psychologic, constitutional and developmental, may account for this capacity to compensate, but the nature of them has not yet been determined. It is on this ability to compensate that therapy and rehabilitation must be based, with an attempt to preserve whatever is left of this capacity and to help the patient to maintain or regain as much of his prestige and social status as possible. Patients in the organic group with senile and arteriosclerotic psychoses derived benefit from tranquillizers and other medication. Those with various mental diseases were treated according to accepted psychiatric therapeutic methods, 2 with electroshock therapy, manic states with Largactil, and reactive depressions with sedatives and supportive psychotherapy. Twenty-five patients with so-called neuroses of later maturity had difficulty in adjusting to the biologic, psychologic, and social facts of aging. Treatment in this group proved the most difficult, and included many physical and medical measures in order to gain the confidence of the patient. Much of the therapy in this group had to be carried out by a social worker.

PRIMARY PULMONARY HYPERTENSION.
Kuida, H.; Dammin, G. J.; Haynes, F. W.; Rapaport, E., and Dexter, L. *Am. J. Med.* **23:** 166 (Aug.) 1957.

Primary pulmonary hypertension is a distinct clinicopathologic entity characterized by pulmonary arterial and right ventricular hypertension. Right ventricular hypertrophy is uniformly present and may or may not be accompanied by right ventricular failure. Hypertension is the result, hemodynamically, of excessive increase in pulmonary vascular resistance and may reflect inself in the pulmonary vessels by a variety of vascular lesions. The pathogenesis of the ultimate vascular lesions remains obscure. The clinical, hemodynamic, and pathologic features of 4 patients with this condition are presented. The clinical findings of cases reported in the literature as well as in these cases show a remarkable uniformity which, in our interpretation, is a reflection of the pulmonary hypertension. Thus, it is difficult, if not impossible, on clinical grounds alone to differentiate this lesion from any of the multitude of conditions in which pulmonary hypertension is a secondary concomitant. Cardiac catheterization has provided valuable information on the pathophysiology of primary pulmonary hypertension and may be of great value in differential diagnosis, particularly in excluding congenital heart disease. The abnormal hemodynamic data that may be demonstrated by this technic, however, are not sufficiently specific to permit one to make a conclusive diagnosis. Such a definitive diagnosis is possible only by necropsy, and even then the exact mechanism may be difficult to define, although it is apparent now that many of the lesions in the pulmonary arteries represent the effects of pulmonary hypertension. In the face of such diagnostic difficulties, and because there is no satisfactory treatment for primary pulmonary hypertension, it is in the patient's best interest that a search for a lesion that can be treated should not be abandoned. (From authors' summary.)

THE EPIDEMIOLOGY OF CORONARY HEART DISEASE. (Seminar on Atherosclerosis.)
Mann, G. V. *Am. J. Med.* **23:** 463 (Sept.) 1957.

Mann reviews factors that tend to distort the statistics on the incidence of coronary heart disease. For example, he points out that almost one-third of the cases may end with sudden death, that these cases will be studied only by the medical examiner, and that in

only a small proportion will a necropsy be performed. The "transference" of cause of death from 7 easily mistaken categories of cause of death to disease of the coronary arteries may account for some of the supposed increase in mortality from coronary heart disease. The practice of certification of cause of death by assigning one prime cause may account for part of the apparent increase, because earlier causes of death are removed by this process. The conclusions reached are as follows: The available evidence indicates that the increase in coronary heart disease revealed by vital statistics is largely artificial. The epidemiologic data suggest the need for laboratory investigation of the role of energy balance and physical activity in the development of coronary atherosclerosis and thrombosis. New epidemiologic data are needed from prospective studies of populations which emphasize certain cultural differences. The literature abounds with uninterpretable retrospective studies, and especially necropsy series. There is a great need among medical scientists for a better appreciation of the advantages of the planned experiment. Epidemiologic data must meet three requirements to be useful: 1) the population studied must be described, so that an independent worker can obtain a comparable group; 2) the methods must be reproducible; and 3) the data must be shown in sufficient detail so that independent analysts can evaluate them. Epidemiology is apt not to be a decisive method for resolution of these problems of chronic disease despite the current popularity of this endeavor. At best, the method may supply a few clues and enough encouragement to gifted people who, by intuitive knowledge and industry, will find the answer in the laboratory. Those who propose that the models of epidemiologic method developed in the study of infectious disease may be directly applied to chronic disease do not perceive the unique obstacles presented by the slow timescale of coronary heart disease.

THE PHYSIATRIC CONTRIBUTION TO GERIATRICS.

McMorrow, K. *J. Michigan State M. Soc.* **56:** 1440 (Nov.) 1957.

Physiatrics is concerned with the evaluation and management of the disabled patient through the use of physical methods and the careful integration of paramedical services. Emphasis is upon the patient rather than upon the disease. Situations in which the physiatrist can be helpful are indicated. Among the contributions that the physiatrist can make to the geriatric patient, improvement in pulmonary ventilation capacity is probably the most valuable. Efficiency in inspiration affects the maximal breathing capacity and residual volume, with an increase in tolerance to fatigue. This applies especially to patients with asthma, emphysema, parkinsonism, and rheumatoid spondylitis. The physiatrist can be helpful in evaluating the work tolerance of cardiac patients and altering it through specific changes in the mechanics of ventilation. He can best appreciate in clinically integrated fashion the metabolic functions of muscle and the effects of muscular action on the efficiency of the heart and lungs. In senile osteoporosis, treatment utilizing the range of motion in the joints will slow the development of a negative nitrogen balance in patients who must remain in bed, but early ambulation is the treatment of choice. An estrogen-androgen combination in a ratio of 15:1 (Nilevar) has facilitated a positive nitrogen balance in elderly patients with osteoporosis. The osteoporosis that results in pathologic fractures following prolonged steroid therapy in rheumatoid arthritis causes pain, but the patient's pulmonary ventilation may also be reduced. The Taylor back brace, often prescribed for use in pathologic fractures of the dorsal spine, has the disadvantage of further immobilization of the costovertebral structures and concomitant reduction in pulmonary ventilation. In low back disorders due to osteoarthritis, a back brace is worthless unless active postural compensation and weight reduction in obese patients are included in the regimen. Because of the psychic element present in obesity, psychiatric assistance or adjustment of the environment may become necessary for successful treatment. Cervical spondylosis may occur in association with osteoarthritis. In any patient with shoulder pain or restriction, examination should include a roentgenogram of the cervical vertebrae and determination of the kinesiology of the cervical muscles, in order to prevent development of periarthritis of the

shoulder secondary to unrecognized cervical spondylosis. Periarthritis of the shoulder also frequently complicates coronary insufficiency and infarction. Treatment consists of passive range-of-motion exercises three times daily. Peripheral vascular insufficiency is primarily a diagnostic problem for the physiatrist. Short-wave diathermy to the low back in order to promote reflex vasodilation is the treatment of choice when arteriolospasm is severe. The physiatrist should be in charge of patients with disabilities due to amputations of the extremities, cardiovascular accidents, and degenerative neurologic conditions with involvement of the whole body. In the case of decubitus ulcers, treatment should include ambulation whenever possible, attention to the protein balance, and the application of a daily erythemal dose of ultraviolet light to the ulcer. Histamine iontophoresis with electrical stimulation of the anterior tibial and calf muscles will promote healing in the case of varicose ulcers with dermatitis. Geriatric patients with fractures also should be under the care of the physiatrist. Early ambulation is desirable in the case of fractures of the lower extremities but the difficulties in achieving it are pointed out. Fractures of the upper extremities require casts but this should not be continued past the time when the bone has healed, lest periarthritic changes and muscle atrophy occur. Much can be accomplished through orthopedic reconstructive procedures and physiatry if patients are permitted a sufficiently long hospital stay. Many of the problems in the management of chronic illness will be solved when it is realized that acceptance of the high direct costs of hospitalization will eliminate some of the problems in the management of chronic illness and disability, including increasing indirect costs.

VALUE OF METRAZOL THERAPY IN THE AGED.

Morrison, B. O. *J. Louisiana State Med. Soc.* **109:** 453 (Dec.) 1957.

Seven patients aged 64 to 85 years with cerebral arteriosclerosis received 6 grains of Metrazol per day for an average of 7.7 months in early disease and an average of 11 months when symptoms were moderate. Seven patients with early arteriosclerosis and 4 with moderate arteriosclerosis improved. They lost, or had a diminution in, their antisocial behavior, cooperated better, were less abusive and depressed, and had better appetites. All except 1 patient with early arteriosclerosis had associated disease, which included heart disease, arrested tuberculosis, Ménière's syndrome, epilepsy, late manifest lues, and psychosis. Two of the 4 patients with moderate arteriosclerosis had coronary artery disease, nutritional illness, and a psychosis. Treatment with Metrazol brought about improvement with regard to all pretreatment symptoms in patients with moderate arteriosclerosis; these symptoms consisted of poor personal hygiene, impaired sensorium, inadequate memory, poor nutrition, and psychosis. As in the first group, the most dramatic improvement occurred in mental outlook. Six patients who failed to improve were markedly arteriosclerotic and, as a result, probably had extensive destruction of brain tissue. In addition, they had many serious complications. Long-term therapy with Metrazol appears to be necessary before any marked change can be anticipated in patients such as those in this study. No side-effects were noted from the prolonged administration of Metrazol.

SYNDROME OF HYPOGAMMAGLOBULINEMIA, SPLENOMEGALY AND HYPERSPLENISM.

Prasad, A. S.; Reiner, E., and Watson, C. J. *Blood* **12:** 926 (Oct.) 1957.

One new case, and the follow-up of 1 case of acquired idiopathic hypogammaglobulinemia associated with splenomegaly and hemolytic anemia due to hypersplenism are presented in detail. Hematologic improvement occurred in both following splenectomy. Both of these patients were also treated with gamma globulin and antibiotics. The first, a 65-year-old woman who had had repeated episodes of pneumonia previously, died of bronchopneumonia. The second patient is alive and has done well. Gamma globulin was discontinued after four months. She is still maintained on antibiotics. The history in this patient indicates that the hypogammaglobulinemia preceded the onset of splenomegaly and hypersplenism. In these cases, as in others reported, these two conditions appear to be the result of reticu-

lum-cell hyperplasia caused by the lack of gamma globulin and resultant repeated infections. The mechanism of production of hypogammaglobulinemia is not as yet known. This syndrome appears, from a review of the literature, to be relatively common. It can and should be recognized because of the possibility of successful management. The serum gamma globulin level should be determined in patients with unexplained hepatosplenomegaly, hypersplenism, and hemolytic anemia.

FURTHER OBSERVATIONS ON PATIENTS WITH MALIGNANT CARCINOID.

Sjoerdsma, A.; Weissbach, H.; Terry, L. L., and Udenfriend, S. *Am. J. Med.* **23:** 5 (July) 1957.

A study of 13 additional cases of metastatic carcinoid showed that vasomotor disturbances, respiratory distress, valvular heart diesase, and diarrhea are associated with the disease. The clinical manifestations vary; some patients with extensive disease do not show all, or even the predominant, manifestations. Prolonged survival has been noteworthy even in patients with ominous signs and symptoms. Malignant carcinoid is being recognized more frequently because of the availability of a simple diagnostic test, the measurement of urinary 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin, elevated blood levels of which are found in carcinoid. The serotonin content of the blood platelets, and the urinary excretion of 5-HIAA, were found to be elevated in carcinoid. Blood values ranged between 0.2 and 0.8 μg. per ml. of plasma. Plasma values for free serotonin varied from insignificant amounts to 2.7 μg. per ml., but they could not be considered valid because of difficulties that exist in the method of determination. No pulmonary arterio-venous difference in the plasma serotonin levels could be demonstrated. Therefore, a hypothesis that such a difference might account for predominantly right heart involvement could not be substantiated. Severe flushing appeared to be accompanied by an increased release of serotonin from the carcinoid, as determined by daily measurements of urinary 5-HIAA. A tracer study in 1 patient with the serotonin precursor 5-hydroxytryptophan in radioactive form made possible the calculation of a tumor pool of 2800 mg. of serotonin, its turnover rate (half-life of five and one-half days), and a tumor mass of 1 to 3 Kg. The finding of significantly low tryptophan fasting plasma levels and low urinary N′-methylnicotinamide in patients with carcinoid supports the hypothesis of a secondary tryptophan deficiency with decreased formation of other substances in the pathogenesis of carcinoid. Psychiatric evaluation showed no characteristic personality changes. This together with the absence of serotonin in the spinal fluid indicates that serotonin does not penetrate into the central nervous system. Administration of reserpine failed to release serotonin from the tumor of a patient given 140 mg. in twenty-five days. It did, however, decrease elevated platelet serotonin levels. The only drug with a therapeutic effect is chlorpromazine. It appears to decrease the frequency and severity of the flushing reaction, allay anxiety, and control nausea when it occurs. It may be that chlorpromazine does not interact with serotonin.

DETERMINATIONS OF SQUALENE IN SEBUM FROM THE FOREHEAD OF PATIENTS WITH SKIN CANCER.

Sobel, H.; Marmorston, J.; Wright, E. T., and Garcia, E. *J. Invest. Dermat.* **29:** 269 (Oct.) 1957.

Squalene, a major constituent of human skin, so alters methylcholanthrene that the end-products of this interaction are no longer carcinogenic. Therefore, squalene in sebum may be a protective agent. An investigation was undertaken to compare the squalene content of the skin of persons with and without carcinoma. The squalene content of the surface fat from the forehead was determined in patients with carcinoma of other parts of the face and neck. The mean age of the control subjects was 67 years and that of all patients with carcinoma, 69 years. Patients with basal-cell carcinoma produced higher levels of squalene, and those with epidermoid carcinoma lower levels, than noncancerous persons.

The latter finding suggests that squalene serves as a protective agent, inasmuch as this is the type of carcinoma that usually is caused by exposure to hydrocarbon carcinogens and excessive exposure to sunlight and roentgen rays. Increased quantities of squalene in basal-cell carcinoma was a surprising finding but consistent with Haythorne's concept that this growth arises from the pilosebaceous apparatus. Hyperplasia has been observed in the sebaceous glands in the forehead of middle-aged and elderly persons. The observation has also been made that the basal cells lining the outer sheath of the hair follicles, sweat ducts, and sebaceous glands are similar to the basal cells of the epidermis and therefore may participate independently or simultaneously in any neoplastic process. Thus, it is possible that basal-cell carcinoma may arise from a hyperplastic environment.

UPPER GASTROINTESTINAL BLEEDING IN THE AGED.

Thompson, W. H., and Leffel, J. M. *J. Indiana State M. A.* **50:** 1337 (Oct.) 1957.

Gastro-intestinal hemorrhage in the aged is a serious situation associated with high operative mortality and requiring the utmost surgical skill in management. Careful observation is required and a medical consultation is obtained for the evaluation of poor-risk patients, as they are likely to have many other complicating diseases. An attempt is made to establish the diagnosis as soon as possible by subjecting the patient to roentgenographic examination by the Hampton technic. Esophagoscopy is performed early, when that procedure is planned. It is recommended that surgery in the aged with gastro-intestinal bleeding be performed as promptly as possible, with the surgeon doing all he can to expedite it. Partial gastric resection including the ulcer is the procedure of choice. In rare instances, ligation of the ulcer, or exclusion of the ulcer and wedge resection may be life-saving in a critical situation; a more definitive procedure can be carried out later. When the site of the hemorrhage cannot be found by careful search of the intestinal tract together with gastrotomy and duodenotomy, a high 75 or 80 per cent gastrectomy is performed. Bleeding occurs most commonly from esophageal varices, a gastric ulcer, or a duodenal ulcer in that order. Among 248 instances of elective surgery for peptic ulcer, the mortality rate was 2 per cent. In contrast, the mortality rate was 27.8 per cent among 36 cases of massive upper gastrointestinal hemorrhage. Approximately 75 per cent of the patients in these two groups who died were over age 60. The postoperative complications causing death were predominantly pulmonary and cardiorenal.

NEWS AND NOTICES

NEW PUBLICATION ORIENTS DOCTORS ON CHANGING NATIONAL HEALTH PATTERNS

Timely statistical 'profiles' on major health problems, ranging from allergic ailments to cardiovascular disease, form the theme of a new monthly publication, "Patterns of Disease." Prepared by Parke, Davis & Company, the publication is being offered as a service to the medical profession.

Major aims of "Patterns" are to provide information which physicians can use to anticipate health problems in their areas; to determine which diseases they will encounter most often among various age groups and in various localities; and to choose fields of specialty most useful to their own communities. For instance, midwestern physicians, reading in the first issue of "Patterns" of the high concentration of older people in their area, may decide to place more emphasis on geriatrics.

Changing national patterns of health can mean changing habits of practice. "Patterns" will familiarize physicians with these changes by presenting in pictograph form statistics on all aspects of commonly encountered medical problems. The publication also incorporates Parke-Davis' "Pediatric Patterns," the only monthy source of information on the incidence of five common communicable childhood diseases, broken down by states and cities. Future issues will deal with such topics as cardiovascular disease, arthritis, allergic diseases, diabetes, and mental health.

The first issue, now being mailed to 140,000 physicians throughout the country, is devoted to the *growing problem of America's aged population*. It deals with such questions as: "Where do our older people live?" "What does our longer life span mean?" "What type of care will the aged require?" "How much will it cost?"

Maximum concentrations of older people, "Patterns" reveals, are in such far-flung areas as the New England states, the Great Plains states, and in Florida, rather than the Gulf states and on the West Coast, as is widely believed.

The publication also stresses the growing number of aged people in our population, especially women. Since 1900, it states, the population of the United States has almost doubled but the number of persons aged 65 and older has more than quadrupled. In 1975 it is estimated that 10 in every 100 Americans will be in the older age group, and 6 of these will be women.

Our life span, says "Patterns," has increased from less than 50 years in 1900 to slightly over 70 now. This rapid increase in life expectancy, however, is coupled with a rise in death rates for the chronic diseases, with heart disease exacting a heavier toll than all other diseases combined. Heart disease, too, ranks as the commonest chronic disease, afflicting well over half of the older age group. Other major health problems in this group include arthritis and obesity.

Who takes care of the aged? Nursing homes rank highest in this respect, as 90 per cent of their population is in the 65-and-over age group, "Patterns"

reports. Next, are institutions for chronic diseases, in which 65 per cent of the beds are occupied by the older age group. The figure is 53.3 per cent for convalescent and rest homes, 21.6 per cent for nervous and mental hospitals, and 18.2 per cent for general hospitals.

The care of the aged imposes a heavy financial drain. Although old people comprise only 9 per cent of the population, they incur 13 per cent of the costs for all private, personal health services. The average aged person spends about $122 per year for medical care as against $78 for the general population.

Because of what lies ahead for the aged, "Patterns" predicts that more demands will be made on specialists in the future. "Severely disabled older persons need medical checkups on the average of once every two months."

"Patterns" stresses, however, that with "adequate care, improvement of health or halting the progression of chronic disease can be expected in 41 per cent of those 65 years and over."

WASHINGTON UNIVERSITY COURSE IN GERIATRIC MEDICINE

The Washington University School of Medicine, Division of Gerontology, will conduct a postgraduate course in Geriatric Medicine with special emphasis on heart disease and the psychosocial problems of later life, to be held at the University, Euclid Avenue and Kingshighway, Saint Louis, Missouri, *Saturday, May 24 and Sunday, May 25, 1958.*

Outstanding speakers from the St. Louis area and authorities from other universities will compose the faculty. Clinical application of the basic principles of disease in later life will be stressed.

There will be no registration fee.

Category I credit will be granted to members of the American Academy of General Practice.

For further information, please write John C. Herweg, M.D., Assistant Dean, Postgraduate Education.